

**Assessment and Behavioural Modulation of  
the Upper Oesophageal Sphincter  
in Healthy Swallowing**

A Thesis Submitted in Partial Fulfilment of the Requirements for the Degree of  
Doctor of Philosophy

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## **Abstract**

Timely and adequate opening of the upper oesophageal sphincter (UES)<sup>1</sup> during swallowing is critical for safe and efficient bolus transfer from the pharynx into the oesophagus. At rest, the occluded UES functions as an important barrier between the pharynx and oesophagus. UES impairment may lead to severe consequences such as aspiration. In clinical practice, the role of speech-language therapists involves comprehensive assessment of UES function and, if indicated, specific treatment. The use of instrumentation is required for diagnostic purposes as the UES is not visible externally. This PhD programme of research involved two studies focussing on instrumental assessment of UES function. One methodological study investigated the potential of new ultrasound technology for evaluation of hyolaryngeal excursion, a biomechanical event of interest in the assessment of UES function. A second methodological study evaluated the current state of practice in the use of high-resolution manometry (HRM) that is an emerging technology in the assessment of pharyngeal and UES pressure. While clinicians rely on optimised instrumental assessment of UES function, rehabilitation approaches that address underlying pathophysiology are as important. There are limited behavioural treatment options for impaired pressure regulation. Hence, studies to explore potential new avenues in the rehabilitation of UES function are necessary. The exploratory study of this PhD research focuses on volitional modulation of UES pressure in healthy subjects to build a foundation for potential future behavioural treatment avenues.

The use of ultrasound allows for radiation-free assessment of hyolaryngeal excursion, a biomechanical event that contributes substantially to UES opening. Reported validity and reliability data are promising for this purpose. Despite this, the use of ultrasound devices has not translated into routine clinical practice for deglutition. Newly developed, pocket-sized ultrasound systems may facilitate clinical translation, but image quality requires evaluation. Thus, validity and reliability testing of this newer technology in the assessment of hyolaryngeal excursion was completed in a cohort of 20 healthy participants. Validity was quantified using correlation analysis to similar measures derived from videofluoroscopic swallowing study. Reliability was evaluated within and across raters as well as over time using the intra-class

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<sup>1</sup> This thesis was prepared using British spelling conventions. However, the acronym 'UES' (upper esophageal sphincter) is strongly represented in the literature, thus UES rather than UOS (upper oesophageal sphincter) was used.

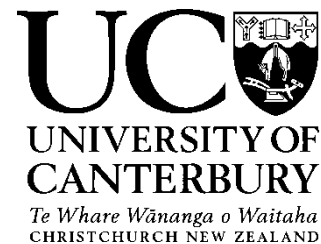
correlation coefficient (ICC) and standard error of measurement (SEM). Findings of insufficient validity and reliability suggest that pocket-sized ultrasound equipment may not yet meet the standards of larger, more expensive ultrasound devices.

Assessment of pressure at the UES may be critical to evaluate underlying pathophysiology of UES dysfunction. The use of pharyngeal HRM in the assessment of pharyngeal swallowing is in early stages; thus, there are limited methodological standards. Yet, methodological aspects of data acquisition and analysis may have a considerable impact on measurement. A systematic review was conducted to summarise and appraise the methodology reported in studies using pharyngeal HRM, with and without impedance, in adult populations. Among the 62 manuscripts that met the inclusion criteria, great variability in reported methodology was apparent. Further, a striking number of manuscripts provided insufficient methodological information. Unfortunately, interpretation of data and eventual development of measurement standards are restricted if reports of methodology are lacking.

There are data to suggest that aspects of UES function, including UES opening duration or pressure at the UES during swallowing, can be *indirectly* altered by volitional manipulation of pharyngeal biomechanics and pharyngeal pressure generation (Hoffman et al., 2012). However, it is unknown whether pressure at the UES can be *directly* modulated. The potential for volitional modulation of pressure at the UES by healthy adults was investigated. Twelve participants attended one-hour training sessions, daily over two weeks. A single follow-up session was completed after a training break of two weeks. One group of participants (n = 6) was asked to volitionally increase and decrease UES resting pressure, the other group of participants (n = 6) was instructed to prolong pressure related UES opening during swallowing. During training, HRM was used as a biofeedback modality; no instruction was purposefully given regarding how to achieve the task goal. The findings suggested the potential for healthy adults to increase UES resting pressure following training. Further, results indicated that participants were able to behaviourally increase pressure related UES opening duration; yet, this was not enhanced by daily training.

This research addresses the ongoing need for optimised instrumental assessment of UES function by exploring the viability of new ultrasound technology for this purpose. Further, data of this programme of research provide a foundation for enhanced use of pharyngeal HRM in the assessment of UES pressure. Finally, this is the first programme to investigate the potential for direct behavioural pressure modulation at the UES in healthy subjects. These data may provide grounds for potential behavioural treatment options for UES impairment.

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Please indicate the chapter/section/pages of this thesis that are extracted from co-authored work and provide details of the publication or submission from the extract comes:

*Chapter 8: Assessment of the UES: A Systematic Review of Pharyngeal HRM/HRIM*

**Winiker K**, Gillman A, Guiu Hernandez E, Huckabee M-L, Gozdzikowska K (2018): A systematic review of current methodology of high resolution pharyngeal manometry with and without impedance. *European Archives of Oto-Rhino-Laryngology*. doi.org/10.1007/s00405-018-5240-9

Please detail the nature and extent (%) of contribution by the candidate:

*K Winiker was primary author of the manuscript (90%); M-L Huckabee, K Gozdzikowska and K Winiker (40%) developed the concept of the manuscript; all authors contributed to manuscript editing (K Winiker 20%). All authors contributed to data extraction and data analysis (K Winiker 50%).*

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- In cases where the candidate was the lead author of the co-authored work he or she wrote the text

Name: *Maggie-Lee Huckabee PhD* Signature:

Date: *10 March 2019*

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## Preface

This PhD thesis followed the referencing style documented in the Publication Manual of the American Psychological Association (6<sup>th</sup> ed.) and conforms spelling recommended by the Oxford Dictionary (<https://www.oxforddictionaries.com/>).

The research of this thesis was carried out between February 2016 and March 2019. During this period, the PhD candidate was enrolled in the Department of Communication Disorders at the University of Canterbury in Christchurch, New Zealand. The research was based at the University of Canterbury Rose Centre for Stroke Recovery and Research and supervised by Prof Maggie-Lee Huckabee, Dr Kristin Gozdzikowska, and Dr Phoebe Macrae. Financial support was provided by the Keith Laugesen Scholarship.

Following aspects of this research have been presented by the PhD candidate at national and international conferences:

**Winiker K**, Gillman A, Guiu Hernandez E, Huckabee M-L, Gozdzikowska K (2017, September). *Pharyngeal high-resolution manometry with/without impedance: A systematic review of current methodology and analysis techniques*. Platform presentation at the European Society for Swallowing Disorders conference, Barcelona.

**Winiker K**, Gozdzikowska K, Guiu Hernandez E, Kwong SL, Macrae P, Huckabee M-L (2017, September). *Volitional control of resting pressure at the upper oesophageal sphincter in healthy adults: An exploratory study*. Poster session presented at the European Society for Swallowing Disorders conference, Barcelona – awarded poster of merit.

**Winiker K**, Gozdzikowska K, Guiu Hernandez E, Kwong SL, Macrae P, Huckabee M-L (2018, September). *Can healthy adults volitionally prolong upper oesophageal sphincter opening during swallowing?* Poster session presented at the European Society for Swallowing Disorders conference, Dublin – awarded poster of merit.

**Winiker K**, Burnip E, Guiu Hernandez E, Huckabee M-L (2018, October). *Reliability of ultrasound measurement for swallowing assessment*. Oral presentation at the Biomouth Conference, Christchurch.



The following manuscript was published during this PhD research:

**Winiker K**, Gillman A, Guiu Hernandez E, Huckabee M-L, Gozdzikowska K (2018): A systematic review of current methodology of high resolution pharyngeal manometry with and without impedance. *European Archives of Oto-Rhino-Laryngology*, 276(3), 631-645.  
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Projected manuscripts from this research programme include:

*Validity and reliability of a pocket-sized ultrasound system in swallowing assessment.*

*The capacity of healthy adults for behavioural manipulation of pressure at the UES.*

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## **List of Abbreviations**

AIMplot	automated impedance manometry analysis
ALS	amyotrophic lateral sclerosis
AMSTAR	assessment for multiple systematic reviews
CI	confidence interval
CN	cranial nerve
CNS	central nervous system
CPG	central pattern generator
CSA	cross-sectional area
CT	computed tomography
DSG	dorsal swallowing group
EMG	electromyography/electromyographic
FOM	floor of mouth muscles
GH	geniohyoid muscles
GH <sup>+</sup>	combined measure of geniohyoid and mylohyoid muscles
HRM	high-resolution manometry
HRIM	high-resolution impedance manometry
ICC	intraclass correlation coefficient
IQR	interquartile range
LAB	left anterior belly of the digastric muscles
MRI	magnetic resonance imaging
NA	not applicable
NR	not reported
PNS	peripheral nervous system
PRISMA	preferred reporting items for systematic reviews and meta-analyses
Q-Q-plot	quantile-quantile plot
RAB	right anterior belly of the digastric muscles
SD	standard deviation
SEM	standard error of measurement
UES	upper oesophageal sphincter
VSG	ventral swallowing group

## **PART I: INTRODUCTION AND LITERATURE REVIEW**

## **1. Introduction**

The UES has an important function at rest and during swallowing. The contracted UES at rest represents a barrier between the pharynx and oesophagus that is critical for protecting the airway from potential refluxate and to prevent passive suction of air into the oesophagus during inspiration (Lang, 2013; S. Singh & Hamdy, 2005). UES function during swallowing involves timely and adequate UES opening to allow for unhindered bolus flow from the pharynx to the oesophagus (Jungheim et al., 2014b). Considering the potential negative impact of UES dysfunction on swallowing safety and efficiency, detailed assessment of UES function is of utmost importance in individuals with suspected UES impairment. Comprehensive evaluation of UES physiology relies on instrumental examination and provides the foundation for specific rehabilitation. The purpose of this research programme was to contribute to an optimised use of instruments in the assessment of UES function and to explore the potential for volitional manipulation of UES function, as current behavioural treatment options are limited.

Part I provides a comprehensive review of the literature. A summary of physiology and neural control of swallowing is provided in Chapter 2 and 3, respectively. The focus of Chapter 4 is the UES; aspects including anatomy, physiology, and neural control of the UES are outlined. In addition, volitional manoeuvres that may alter UES function during swallowing are reviewed. Chapter 5 details modalities that may be used for instrumental examination of UES function including videofluoroscopy, ultrasound, HRM, and high-resolution impedance manometry (HRIM). Advantages and limitations of each instrumentation in the assessment of UES function are discussed. Lastly, Chapter 6 provides an outline of the objectives and hypotheses for the studies that constitute this research programme.

Part II of this work presents methodological studies focusing on instrumental modalities for UES assessment. Evaluation of hyolaryngeal excursion is of significance in the assessment of UES function as this biomechanical event elicits UES opening. Application of ultrasound in the assessment of hyolaryngeal excursion has been documented in the literature. Despite advantages of this radiation-free procedure, established ultrasound devices have not translated into clinical routine for this purpose. Newly developed pocket-sized ultrasound systems may allow for increased clinical applicability. Chapter 7 details studies exploring validity and reliability of a pocket-sized ultrasound device in the assessment of swallowing measures. This will clarify the potential for clinical application of this new technology for radiation-free assessment of hyolaryngeal excursion.

Pressure analysis is a further component of comprehensive UES assessment. Chapter 8 presents a systematic review of reported methodology of studies using pharyngeal HRM with and without impedance in the assessment of pharyngeal and UES pressure. At present, pharyngeal HRM has limited methodological standards available. Thus, there is a need for an in-depth analysis of current methodological practice to guide further development of pharyngeal HRM/HRIM.

Part III presents exploratory studies. These studies were driven by the desire to explore the potential for behavioural modulation of UES function in healthy subjects. Historically, pharyngeal swallowing was considered a brainstem-controlled reflex (Ertekin & Aydogdu, 2003; Vasant & Hamdy, 2013). Yet, an increasing body of research highlights the role of supratentorial structures in the neural control of swallowing (Humbert & German, 2013; A. J. Miller, 2013). Involvement of structures, such as the cortex, in the control of swallowing (Michou & Hamdy, 2009), suggests an increased potential for volitional modulation of pharyngeal swallowing. Prior research has proposed that intra-swallow UES opening can be *indirectly* modulated in healthy subjects by alteration of pharyngeal biomechanics during execution of the Mendelsohn manoeuvre (Hoffman et al., 2012). However, there is no previous research reporting on the potential of adults to *directly* manipulate UES function. This study explored whether healthy adults have the potential to volitionally modulate pressure at the UES at rest and during swallowing. If UES pressure can be directly manipulated, impairment of pressure regulation could potentially be more specifically treated in patients with UES dysfunction.

Finally, Part IV provides concluding notes regarding the studies that constitute this research programme. This PhD thesis explores new avenues in the evaluation of hyolaryngeal excursion, a biomechanical event relevant for UES opening and provides a contribution for refined use of pharyngeal HRM/HRIM in the analysis of UES pressure. Further, exploratory data about the potential of healthy subjects for direct manipulation of UES function provide a foundation for future research evaluating purposeful pressure modulation in dysphagic patients to clarify if the specificity in behavioural treatment for UES impairment may be increased.

## **2. Physiology of Swallowing**

Swallowing serves a vital alimentary function by moving food or liquid from the mouth to the stomach (Jean, 2001). Further, approximately 1.0 – 1.5 litres of saliva are swallowed per day (Matsuo & Palmer, 2013). While awake subjects swallow saliva approximately once per minute, swallowing frequency is decreased during sleep and may be increased during intake of food and liquid (Dodds, Stewart, & Logemann, 1990).

Swallowing is a dynamic and complex sensorimotor neuromuscular process involving a sequence of highly coordinated events (Dodds et al., 1990; Vasant & Hamdy, 2013). A concerted and rapid sequence of muscle activations and inhibitions, continuous integration of sensory information, and pressure regulation are components that constitute swallowing (Jean, 2001). Swallowing physiology is discussed based on a common division of deglutitive swallowing into separate stages, including the pre-oral, oral, pharyngeal, and oesophageal phase of swallowing (Daniels & Huckabee, 2014; Fuller, Pimentel, & Peregoy, 2012; S. M. Shaw & Martino, 2013). Of note, this classification is artificial and serves exclusively descriptive purposes. Interrelations between separate stages are important to acknowledge (Ertekin & Aydogdu, 2003; A. J. Miller, 2013).

### **2.1. Pre-oral Phase**

Prior to acceptance of food and liquid into the mouth, several sensory-induced events occur in preparation for swallowing (Ebihara et al., 2006). Olfactory stimulation using black pepper oil has been found to be associated with reduced latency of the swallowing response in older patients with history of stroke (Ebihara et al., 2006). Cortically processed olfactory and visual stimuli of the bolus are associated with activation of salivary flow (Leopold & Kagel, 1997). Saliva volume and saliva flow rate have been found to be related with initiation of pharyngeal swallowing (Rudney, Ji, & Larson, 1995). A further event that may occur in the preingestive phase of swallowing is adduction of the vocal cords by contraction of the lateral cricoarytenoids, transverse arytenoids, and thyroarytenoids as an early airway protection mechanism (Daniels & Huckabee, 2014; S. M. Shaw & Martino, 2013).

### **2.2. Oral Phase**

Acceptance of food or liquid into the oral cavity marks the start of the oral phase. Food intake requires involvement of the lips (orbicularis oris); further, retraction of facial muscles including the risorius, zygomaticus, and quadratus labi superioris may be necessary for successful



acceptance of larger boluses (Daniels & Huckabee, 2014). Opening of the mouth is accomplished by relaxation of the jaw-closer muscles and by depression of the mandible through contraction of the anterior belly of the digastric, geniohyoid, lateral pterygoid, and mylohyoid.<sup>2</sup> For mouth closure following food intake, elevation of the mandible is attained by contraction of the masseter, medial pterygoid, and temporalis (Fuller et al., 2012).

Upon bolus acceptance, different closing mechanisms occur to contain food or liquid in the oral cavity, preventing the bolus from leaking anteriorly and reducing the amount of bolus spilling prematurely posteriorly into the pharynx (Ertekin & Aydogdu, 2003; Matsuo & Palmer, 2013). Anteriorly, a lip seal and closure of the anterior sulcus is attained through activation of the orbicularis oris (Cichero, 2006; Gay, Rendell, Spiro, Mosier, & Lurie, 1994). The lips typically remain closed until termination of swallowing (Logemann, 1998). Posteriorly, the oral cavity is closed by approximation of tongue and palate by contraction of the palatoglossus and styloglossus (Daniels & Huckabee, 2014; Logemann, 1998). The tongue and buccinator muscles act jointly to avoid food escaping into the lateral sulci (Abd-El-Malek, 1955; Logemann, 1998). Additionally, the tongue shapes around the bolus to avoid spread within the mouth. The bolus is held between tongue and hard palate or on the anterior floor of the mouth (Logemann, 1998).

While swallowing of saliva or liquids requires minimal bolus formation, size and consistency of solid foods need to be modified to build a bolus suitable for swallowing (Sasegbon & Hamdy, 2017). Positioning of bolus between the teeth for mastication is achieved by engagement of the buccinator (Abd-El-Malek, 1955; Cichero, 2006) and the tongue (Matsuo & Palmer, 2008; S. M. Shaw & Martino, 2013). Mastication requires movement of the mandible by activation of the masseter, temporalis, medial and lateral pterygoid (Cichero, 2006; S. M. Shaw & Martino, 2013). During bolus preparation, a high level of coordination is required between movements of mandible, tongue, and hyoid bone (Matsuo & Palmer, 2008, 2013; A. J. Miller, 2013). Formation of a cohesive bolus relies on activity of the tongue. Further, saliva assists bolus formation (Leopold & Kagel, 1997). Saliva is produced primarily

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<sup>2</sup> For ease of communication, this text refers to all corticobulbar muscles activated during swallowing in their single form; although, it is acknowledged that they are all bilaterally represented and activated, except where otherwise specified.

by the sublingual, submandibular and parotid glands (Sasegbon & Hamdy, 2017; S. M. Shaw & Martino, 2013).

Upon completion of mastication and bolus formation, the bolus is kept between superior tongue surface and hard palate (Sasegbon & Hamdy, 2017; S. M. Shaw & Martino, 2013). Then, the bolus is squeezed posteriorly through gradually increasing contact of tongue and palate (Matsuo & Palmer, 2008; S. M. Shaw & Martino, 2013) by activation of the intrinsic (verticalis, longitudinal, transverse) and extrinsic tongue muscles (hyoglossus, styloglossus, genioglossus). The contact of the tip of the tongue and the sides of the tongue with the alveolar ridges persists during bolus transport (Logemann, 1998). For transfer of the bolus to the pharynx, the tongue base drops from the elevated position by relaxation of the palatoglossus (Daniels & Huckabee, 2014). The posterior part of the tongue base is pulled down by contraction of the hyoglossus and genioglossus (Daniels & Huckabee, 2014; Dodds et al., 1990). The duration of the oral phase for liquids is about one second; yet, it can be considerably longer for heavier consistencies (Cichero & Halley, 2006).

### **2.3. Pharyngeal Phase**

Once the bolus contacts the region of the faucial pillars (Logemann, 1998; A. J. Miller, 2013; S. M. Shaw & Martino, 2013), the swallowing response is initiated from sensory stimulation of the glossopharyngeal nerve and the internal branch of the superior laryngeal nerve of the vagus (A. J. Miller, 2008). At this point, the pharyngeal space transitions from a primarily respiratory tract to a digestive tract (A. J. Miller, 1999). Immediately prior to or synchronous with initiation of the swallowing response, the true and false vocal folds, as well as the aryepiglottic folds are adducted to close the airway entrance (S. M. Shaw & Martino, 2013). Given the utmost importance of airway protection during swallowing, it is not surprising that closure of the vocal cords is a very early event during swallowing, potentially occurring even before onset of swallowing, and vocal cord opening occurs last during pharyngeal swallowing (Daniels & Huckabee, 2014; Dodds et al., 1990).

With passage of a bolus at the velopharyngeal port, the nasal cavity is sealed to prevent the bolus from entering the nasal cavity and to optimise pressure conditions across oral, pharyngeal and oesophageal cavities. This velopharyngeal closure is attained by the elevated soft palate through activation of the levator veli palatini and musculus uvulae and with contribution of the superior pharyngeal constrictor (Dodds et al., 1990; Logemann, 1998; Matsuo & Palmer, 2008). As the bolus tail arrives at the tongue base or at the valleculae, the tongue moves

backwards and contacts the pharyngeal wall that is bulging anteriorly (Logemann, 1998). This base of tongue to posterior pharyngeal wall approximation is attained by contraction of the styloglossus, stylohyoid, posterior belly of the digastric, and glossopharyngeus (Daniels & Huckabee, 2014).

With the mandible being stabilised by contraction of the jaw closer muscles, an excursion of the hyolaryngeal complex in superior and anterior direction commences. Hyoid displacement is attained by contraction of the submental muscles including the mylohyoid, geniohyoid, anterior and posterior belly of the digastric, and stylohyoid (Dodds et al., 1990; A. J. Miller, 2008; S. M. Shaw & Martino, 2013). The larynx is raised towards the hyoid by contraction of the thyrohyoid muscle (Cichero, 2006; Fuller et al., 2012; Ludlow, 2005). A potential contribution of the longitudinal pharyngeal muscles (stylopharyngeus, palatopharyngeus, and salpingopharyngeus) to hyolaryngeal displacement has been suggested (Pearson, Hindson, Langmore, & Zumwalt, 2013; Pearson, Langmore, Yu, & Zumwalt, 2012; Pearson & Zumwalt, 2014). Due to the diverse connections of the mobile hyolaryngeal unit with other structures involved in swallowing including the mandible and the cricopharyngeus, the hyolaryngeal excursion assists in airway protection and UES opening (Daniels & Huckabee, 2014).

The effects of hyolaryngeal excursion on airway protection involve supraglottic shortening and epiglottic deflection. Through the elevation of the larynx, the supraglottic space is shortened and the larynx is concealed by the base of tongue, one mechanism to protect the airway entrance (Daniels & Huckabee, 2014; Logemann, 1998). Because the epiglottis is anchored inferiorly behind the thyroid notch, thyrohyoid approximation contributes to epiglottic deflection by compressing tissue between the epiglottis and thyroid notch (Fuller et al., 2012; Vandaele, Perlman, & Cassell, 1995). While the epiglottis remains in a horizontal plane in most subjects, it may be further inverted in others (Ekberg & Sigurjónsson, 1982). The deflected epiglottis seals the entrance to the larynx during swallowing (Kendall, 2008; Vandaele et al., 1995). There are additional mechanisms other than vocal fold closure, supraglottic shortening and epiglottic deflection that contribute to airway protection. The arytenoids tilt anteriorly, thereby approximating the base of the epiglottis to close the inlet to the airway (Dodds et al., 1990; Kendall, Leonard, & McKenzie, 2004; Logemann, 1998). Further, supraglottic structures, such as the aryepiglottic folds, converge. This approximation contributes to laryngeal vestibule closure (Cichero, 2006). Lastly, there is a brief cessation of breathing during swallowing; a median apnoea duration of one second has been found in a study by Martin-Harris and colleagues (2005).

The displacement of the hyolaryngeal complex further assists in UES opening due to the direct and indirect connection of the laryngeal cricoid and thyroid cartilage with the UES, respectively (Jacob, Kahrilas, Logemann, Shah, & Ha, 1989). Hyolaryngeal movement applies traction forces on the cricoid, thereby pulling the cricoid away from the pharyngeal wall and eliciting UES opening (Cook et al., 1989; Dodds et al., 1990; Jacob et al., 1989; Kendall, 2008). An in-depth discussion of UES opening during swallowing follows in section 4.2.2.

Hyolaryngeal movement further facilitates pharyngeal bolus transport. Through the forward movement of the hyolaryngeal complex, the pharyngeal space increases, facilitating bolus flow through the pharynx. Additionally, widening of the hypopharynx results in a pressure decrease in front of the bolus that supports bolus transport (Kendall, 2008; S. M. Shaw & Martino, 2013). Closure of the laryngeal aditus leads to increased pressure at the larynx. This pressure guides the bolus away from the laryngeal inlet (Kendall, 2008). Further, pharyngeal bolus transport is supported by the tongue that pushes in posterior and inferior direction (Kahrilas, Logemann, Lin, & Ergun, 1992) and by sequential horizontal contraction of the pharyngeal constrictors (superior, middle, and inferior) (Kahrilas et al., 1992; J. L. Miller & Watkin, 1997; Palmer et al., 1988). Through contraction of the pharyngeal longitudinal muscles (glossopharyngeus, palatopharyngeus, stylopharyngeus, salpingopharyngeus), the pharynx is shortened. Thus, the volume of the pharynx is reduced and the distance for a bolus to travel is decreased (Daniels & Huckabee, 2014; Dodds et al., 1990; Kahrilas et al., 1992). Following bolus passage through the UES, the UES contracts (Jacob et al., 1989). The time it takes for the bolus to be transported through the pharynx is less than one second; yet, the duration is volume dependent (Logemann, 1998).

#### **2.4. Oesophageal Phase**

The oesophageal phase commences once the bolus has passed the UES and entered the oesophagus. The predominantly striated muscle fibres of the cervical oesophagus (Staller & Kuo, 2013) contribute to the UES. Further, the oesophagus is composed of longitudinal and circular striated and smooth muscles. These muscles act together in a coordinated way to transport bolus to the lower oesophageal sphincter by peristaltic movements (A. J. Miller, 1999; Sasegbon & Hamdy, 2017). In sequential swallowing, the peristaltic wave typically occurs only after the last swallow (Jean, 2001). Once relaxation of the lower oesophageal sphincter is triggered, the bolus is driven toward the stomach by the force of the peristaltic wave. Remaining residue in the oesophagus are cleared by secondary peristaltic waves (S. M. Shaw & Martino, 2013). The oesophageal transit lasts about 8 to 20 s (Logemann, 1998).

### 3. Neural Control of Swallowing

The peripheral and central nervous system (PNS, CNS, respectively) are involved in neural control of swallowing (Neuhuber & Bieger, 2013). Peripheral structures of the head and neck are connected with the brainstem, component of the CNS, via cranial nerves (CN), that are part of the PNS (Bhatnagar, 2013). While the nuclei of the CNs are located in the brainstem, other structures that constitute the CNS, such as the cortex and cerebellum, are also involved in neural control of swallowing (Daniels & Huckabee, 2014).

#### 3.1. Peripheral Control of Swallowing

Sensory and/or motor information is carried by CNs. In the region of the oral cavity, pharynx, and larynx, the population of sensory receptors is very rich as compared to other parts of the human body. Upon excitation of these receptors, sensory CNs carry information to the CNS via afferent pathways. Sensory information may concern taste or mechanical pressure, for example. This information is critical for modulation of motor aspects of swallowing (Bhatnagar, 2013; A. J. Miller, 1999). Motor CNs send commands from the brain, via efferent pathways, to more than 30 peripheral muscles of the head and neck that are involved in swallowing (Bhatnagar, 2013; Johns, 2014; S. M. Shaw & Martino, 2013). The olfactory nerve (CN I) and the optic nerve (CN II) are sensory-only nerves (Daniels & Huckabee, 2014). The trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), and vagus nerve (X) have both sensory and motor branches while the hypoglossal nerve (CN XII) is a motor-only nerve. Further, muscles involved in swallowing are innervated by ansa cervicalis (cervical spinal nerves 1 and 2) (Dodds et al., 1990). Notably, disagreement exists regarding the components of ansa cervicalis (Chhetri & Berke, 1997).

During the pre-oral phase of swallowing, the *olfactory nerve (CN I)* and the *optic nerve (CN II)* are stimulated by smell and visual perception of food, respectively. Primary salivary glands may be stimulated to produce saliva; these glands are innervated by two CNs. The chorda tympani of the *facial nerve (CN VII)* supplies the sublingual and submandibular glands; the *glossopharyngeal nerve (CN IX)* innervates the parotid gland (Daniels & Huckabee, 2014). The *vagus nerve (CN X)* controls the inter- and cricoarytenoid muscles; contraction of these muscles results in vocal cord adduction for early protection of the airway.

The oral phase of swallowing is controlled by CN V, VII, IX, X, XII, and ansa cervicalis. Sensory information from the mucosa of the mouth, gums, and anterior two-thirds of the tongue is carried by the mandibular branch of the *trigeminal nerve (CN V)* (Wilson-Pauwels &

Akesson, 2001). The maxillary branch of CN V provides sensory information from the teeth, hard palate, and anterior proportion of the soft palate. Further, stimulation of afferent fibres of the maxillary branch of CN V contributes to initiation of the swallowing response upon completion of the oral stage of swallowing (Jean, 2001). Motor fibres of the mandibular branch of CN V control the mylohyoid and anterior belly of the digastric (Daniels & Huckabee, 2014; Wilson-Pauwels & Akesson, 2001); these muscles are relevant to jaw opening for bolus acceptance given the hyoid is stabilised (S. M. Shaw & Martino, 2013). Further, motor fibres of CN V innervate the masticatory muscles (Wilson-Pauwels & Akesson, 2001) and the tensor veli palatini (S. M. Shaw & Martino, 2013). Other than CN V, the *facial nerve (CN VII)* provides sensory and motor information during the oral phase of swallowing. The sensory branch of CN VII carries gustatory information from the anterior two-thirds of the tongue (Wilson-Pauwels & Akesson, 2001). Motor fibres supply the orbicularis oris and facial muscles that contribute to mouth opening (Daniels & Huckabee, 2014). Further, the buccinator (Wilson-Pauwels & Akesson, 2001), as well as the stylohyoid and posterior belly of the digastric, are innervated by CN VII. These muscles assist with bolus containment in the oral cavity (S. M. Shaw & Martino, 2013; Wilson-Pauwels & Akesson, 2001). Sensory and motor information are further carried by the *glossopharyngeal nerve (CN IX)* and the *vagus nerve (CN X)*. Excitation of fibres of CN IX and X contribute to elicitation of the swallowing response (Jean, 2001). CN IX carries tactile information of the soft palate and adjacent pharyngeal wall, faucial arches, and posterior third of the tongue. Further, it provides information about taste of the posterior third of the tongue and oral cavity (Daniels & Huckabee, 2014; A. J. Miller, 1999; Wilson-Pauwels & Akesson, 2001). Motor fibres of the *pharyngeal plexus (CN IX and X)* control the palatoglossus. Contraction of this muscle results in approximation of tongue and palate while relaxation is required for bolus transfer to the pharynx (Daniels & Huckabee, 2014). The *hypoglossal nerve (CN XII)* innervates the intrinsic and extrinsic tongue muscles (Daniels & Huckabee, 2014; A. J. Miller, 1999; Wilson-Pauwels & Akesson, 2001). While activation of the intrinsic muscles allows manipulating the tongue contour, the extrinsic muscles change the lingual position within the oral cavity. Contraction of the styloglossus is relevant for tongue-palate approximation while the genioglossus and hyoglossus contract to pull the tongue base downwards for bolus transfer into the pharynx (Daniels & Huckabee, 2014). Lastly, *ansa cervicalis* controls the geniohyoid and the anterior strap muscles including the thyrohyoid muscle. Contraction of the geniohyoid results in depression and retraction of the mandible (S. M. Shaw & Martino, 2013) given the jaw closers are relaxed and the hyoid is stabilised (Daniels & Huckabee, 2014).

The pharyngeal stage of swallowing is controlled by CN V, VII, IX, and X. The *trigeminal nerve (CN V)* supplies the anterior belly of the digastric and the mylohyoid. Through contraction of these muscles, the hyoid is pulled anteriorly given the mandible is stabilised (Daniels & Huckabee, 2014; S. M. Shaw & Martino, 2013); this movement is critical to open the UES (Jacob et al., 1989). As stated above, the *facial nerve (CN VII)* supplies the posterior belly of the digastric and the stylohyoid (A. J. Miller, 1999); these muscles lift and pull the hyoid backwards during pharyngeal swallowing (Daniels & Huckabee, 2014). Sensory fibres of the *pharyngeal plexus (CN IX and X)* carry information from the oro- and hypopharynx while motor fibres supply the levator veli palatini, glossopharyngeus, salpingopharyngeus, palatopharyngeus, and the pharyngeal constrictors. Contraction of the levator veli palatini results in velopharyngeal closure. By contraction of the glossopharyngeus, the tongue is pulled towards the pharyngeal wall while the salpingopharyngeus and palatopharyngeus contribute to pharyngeal shortening. The middle pharyngeal constrictor assists with lifting and pulling the hyoid backward; sequential contraction of the superior, middle, and inferior constrictor is relevant for bolus clearance (Daniels & Huckabee, 2014). The innervation pattern of the cricopharyngeus, the principal component of the UES, is still being discussed in the literature. Nerves that may supply the cricopharyngeus include fibres of the pharyngeal plexus, the laryngeal recurrent nerve (Sasaki, Sims, Kim, & Czibulka, 1999), and the external branch of the superior laryngeal nerve (Uludag, Aygun, & Isgor, 2017). Further details regarding the innervation of the cricopharyngeus are provided in section 4.3. While the cricopharyngeus is tonically contracted at rest, termination of this tonic activation is required for UES opening. Sensory information of the pharynx and larynx is provided by the *vagus nerve (CN X)* (Wilson-Pauwels & Akesson, 2001). Further, motor fibres of CN X innervate the inter- and arytenoid as well as cricoarytenoid muscles that are relevant for adduction of the vocal folds (Daniels & Huckabee, 2014). Lastly, *ansa cervicalis* controls the geniohyoid, thyrohyoid, and the anterior strap muscles. The geniohyoid assists in anterior traction of the hyoid while contraction of the anterior strap muscles, mainly of the thyrohyoid, result in supraglottic shortening (Daniels & Huckabee, 2014).

Vagal pathways play a role in the innervation of the oesophagus (Jean & Dallaporta, 2013; L. S. Miller et al., 2013; Yazaki & Sifrim, 2012). Additionally, the oesophagus receives intrinsic innervation through the enteric nervous system (Staller & Kuo, 2013).

### **3.2. Central Control of Swallowing**

Historically, research on neural control of swallowing was based on animal studies and intraoperative human studies. Data from these studies collectively suggested that swallowing depended on reflexive mechanisms in the brainstem (Neuhuber & Bieger, 2013; Vasant & Hamdy, 2013). However, caution should be taken in the interpretation of animal studies as many of these studies were based on electrical stimulation of swallowing. Further, the use of anaesthesia is common in animal studies; thus, swallowing may be significantly altered (Lang, 2009). Application of new technology such as positron emission tomography and functional magnetic resonance imaging has changed the understanding of how human swallowing is controlled (Jean & Dallaporta, 2013; Rangarathnam, Kamarunas, & McCullough, 2014; Vasant & Hamdy, 2013). It is now recognised that swallowing is a highly complex and dynamic function, that is controlled not only by the brainstem but by diverse cortical and subcortical structures (Ertekin & Aydogdu, 2003; Humbert & German, 2013; A. J. Miller, 2013). The interactions between the various neural mechanisms within the widespread neural network can be described as a model of circuitry (Neuhuber & Bieger, 2013). Even though an increasing body of research about neural control of swallowing exists, the complex interactions are not yet entirely clear (Ertekin & Aydogdu, 2003; Rangarathnam et al., 2014).

#### **3.2.1. Brainstem Control of Swallowing**

The brainstem houses the nuclei of five CNs that are critical for swallowing. The motor and sensory nucleus of CN V and the motor nucleus of CN VII are located in the pons. The medulla houses the motor nucleus of CN XII, the nucleus tractus solitarius, and the nucleus ambiguus. The nucleus tractus solitarius is primary sensory nucleus for CN VII, CN IX, and CN X. The nucleus ambiguus is primary motor nucleus for CN IX and CN X (Daniels & Huckabee, 2014; Jacobson & Marcus, 2011; Rangarathnam et al., 2014).

Based on animal studies, it has been suggested that a bilateral central pattern generator (CPG) in the medulla is responsible for generation of the elementary motor plan and the sequential patterns of swallowing (Daniels & Huckabee, 2014; Ertekin & Aydogdu, 2003; Jean, 2001; Jean & Dallaporta, 2013; S. M. Shaw & Martino, 2013). The concept of a CPG, in general, suggests that reflexive motor patterns can be generated without afferent input. However, these patterns can be modulated by afferent inputs or by descending pathways from centres located superior in the neuraxis (Jacobson & Marcus, 2011). Notably, afferent inputs are needed for elicitation of swallowing (Jean, 2001). Previously, the swallowing CPG was conceptualised as



a swallowing centre (Jean, 2001; Jean & Dallaporta, 2013; Neuhuber & Bieger, 2013). However, the idea of a swallowing centre implies a distinct anatomical area. Thus, current descriptions of the CPG are rather functional than anatomical (Jean & Dallaporta, 2013). The CPG encompasses activity of different pools of neurons including interneurons or premotor neurons, sensory neurons (nucleus tractus solitarius), and motor neurons (nucleus ambiguus) (Jean & Dallaporta, 2013).

One group of interneurons that constitutes the CPG is located dorsally in the medulla oblongata. This dorsal swallowing group (DSG) is formed by neurons within the nucleus tractus solitarius and the reticular formation (Ertekin & Aydogdu, 2003; Jean, 2001; Jean & Dallaporta, 2013). The other main group of interneurons, the ventral swallowing group (VSG), is located ventrally within the medulla oblongata next to the nucleus ambiguus. The DSG receives afferent input from the periphery. Its ‘generator neurons’ (Ertekin & Aydogdu, 2003) are considered to be responsible for triggering the swallowing reflex as well as for timing and sequencing the swallowing events (Daniels & Huckabee, 2014; Jean, 2001). The DSG is directly connected to the VSG and transmits the generated pattern to this group of neurons (Jean & Dallaporta, 2013). The VSG consists of switching neurons that connect to motoneurons and preganglionic neurons. Thus, the sequential drive generated in the DSG is distributed to different motoneurons and preganglionic neurons (Ertekin & Aydogdu, 2003; Jean, 2001; Jean & Dallaporta, 2013). Activation and regulation of the CPG occur through supramedullary inputs and afferent sensory inputs from the periphery (Jean & Dallaporta, 2013). Sensory inputs are relevant not only for initiation of swallowing but also for accommodation of the swallowing motor pattern to characteristics of a bolus such as its consistency, volume, or texture (Neuhuber & Bieger, 2013).

### ***3.2.2. Cortical Control of Swallowing***

Ingestive swallowing requires cortically processed sensory information and cognitive input to modulate the brainstem motor plan; these cortical inputs allow accommodation of the basic motor plan for varied foods and fluids (Daniels & Huckabee, 2014; Jean, 2001; Michou & Hamdy, 2009). Supratentorial regions that have been identified to modulate the swallowing pattern include the precentral and postcentral gyrus, premotor area, supplementary motor area, anterior cingulate gyrus, operculum, insula, precuneus, cuneus, prefrontal area, temporal and frontal cortex, internal capsule, association areas, thalamus, and basal ganglia (Daniels & Huckabee, 2014; Rangarathnam et al., 2014).

The critical role that cortical and subcortical structures play in neural control of swallowing has been evidenced in studies using functional brain imaging techniques (Ertekin, 2011; Michou & Hamdy, 2009; Vasant & Hamdy, 2013) such as magnetic resonance imaging (MRI) (Gonzalez-Fernandez, Kleinman, Ky, Palmer, & Hillis, 2008), functional magnetic resonance imaging (Hamdy et al., 1999; Humbert et al., 2009; Kern, Jaradeh, Arndorfer, & Shaker, 2001; Mosier & Bereznaya, 2001), positron emission tomography (Zald & Pardo, 1999), and magnetic encephalography (Dziewas et al., 2009; Watanabe, 2004). Transcranial magnetic stimulation (Hamdy et al., 1996) has been successfully used to study neural pathways. Further, data from patients after cortical stroke (Martin & Sessle, 1993; Michou & Hamdy, 2009; A. J. Miller, 1999; Vasant & Hamdy, 2013), patients with Alzheimer's disease (Humbert et al., 2010), or patients with amyotrophic lateral sclerosis (ALS) (Teismann et al., 2011) provide evidence for the critical role of the cortex in swallowing. Gonzalez-Fernandez and colleagues (2008) studied patients with acute ischemic stroke in the supratentorial region using MRI. Their study provides evidence that damage to the internal capsule may be associated with development of dysphagia. The internal capsule contains fibres that connect cortex and brainstem (Scarborough, Waizenhofer, Siekemeyer, & Hughes, 2010); thus, indicating the important relationship between cortical areas and brainstem. Notably, in the study by Gonzalez-Fernandez and colleagues (2008), dysphagia was defined clinically rather than physiologically. The increasing body of research documenting the significance of supratentorial structures in neural control of swallowing is relevant for the ongoing debate regarding the potential for voluntary control of swallowing.

While voluntary control of aspects of the oral stage of swallowing is recognised (Malandraki & Robbins, 2013), pharyngeal swallowing was historically considered mainly involuntary (Belafsky & Lintzenich, 2013). Yet, considering involvement of subcortical and cortical structures in neural control of swallowing, the potential for purposeful manipulation of pharyngeal swallowing is a subject of increasing interest (Robbins et al., 2008). Volitional manipulation of pharyngeal swallowing has been studied for different swallowing manoeuvres. As stated by Logemann (1998) "swallow manoeuvres are designed to place specific aspects of pharyngeal swallow physiology under voluntary control" (p. 183). Prior research has shown that behavioural manipulation of the swallowing response can be achieved primarily by increasing effort (Bülow, Olsson, & Ekberg, 1999; Doeltgen, Ong, Scholten, Cock, & Omari, 2017; Hind, Nicosia, Roecker, Carnes, & Robbins, 2001; Hiss & Huckabee, 2005; Hoffman et al., 2012; Huckabee, Butler, Barclay, & Jit, 2005; Witte, Huckabee, Doeltgen, Gumbley, &

Robb, 2008) or increasing duration (Bodén, Hallgren, & Hedström, 2006; Doeltgen et al., 2017; Inamoto et al., 2018; Kahrilas, Logemann, Krugler, & Flanagan, 1991; Logemann & Kahrilas, 1990). Further, there are data to suggest that healthy adults have the potential to volitionally prolong the intra-swallow closure of the laryngeal vestibule if provided with combined feedback on performance and outcomes (Macrae, Anderson, Taylor-Kamara, & Humbert, 2014). While volitional manipulation of the pharyngeal phase in its entirety has been subject in numerous studies, there is little known whether single aspects of the swallowing response can be volitionally modulated.

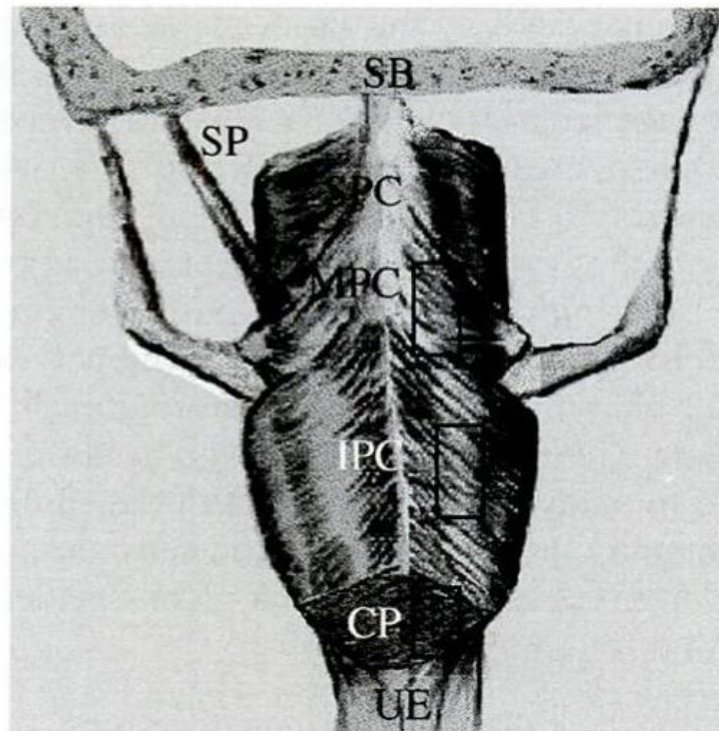
Huckabee, Lamvik, and Jones (2014) reported on the capacity for volitional manipulation of pharyngeal pressure generation in a cohort of patients with dysphagia. The patients included in this study presented with “pharyngeal mis-sequencing” (p. 154). This is a pathological feature characterised by simultaneous pressure generation in the upper and lower pharynx, resulting in symptoms including impaired bolus transport through the pharynx, nasal redirection of bolus, and aspiration. Using pharyngeal manometry as visual biofeedback, patients were asked to volitionally increase the latency between the proximal and distal pressure wave tracings. Following intensive rehabilitation, the temporal separation between pressure generation in the upper and lower pharynx increased considerably. Based on this study, Lamvik and colleagues (2015) reported on the capacity of healthy adults to volitionally manipulate a select aspect of the pharyngeal swallowing response, the timing of pharyngeal pressure. The study demonstrated that during intensive training using manometric biofeedback, participants were able to reduce the latency of pressures generated in the upper and lower pharynx without altering the total swallowing duration during training. However, analysis of post-training swallows revealed that participants modulated the pharyngeal response cumulatively, by swallowing faster, rather than modulating in isolation. Yet, without wider assessment of swallowing features, it is difficult to know if further aspects of swallowing were modulated. Hence, there is limited evidence for volitional control of a discrete component of swallowing. Yet, existing data form a good basis by which future studies can be planned to investigate this phenomenon. Future research is needed as a single study is insufficient to evaluate the potential for discrete volitional control in healthy subjects. Not only the innervation of different components of pharyngeal swallowing is different, but the fact that aspects of pharyngeal swallowing can be impaired in isolation suggests that each component should be considered separately (Daniels & Huckabee, 2014).

## **4. The Upper Oesophageal Sphincter (UES)**

The UES is an anatomical complex located at the transition from the pharynx to the oesophagus, comprising portions of both structures (Jungheim et al., 2014a; S. Singh & Hamdy, 2005). It borders the spinal column (C5 - C6) posteriorly and the cricoid cartilage anteriorly (Jungheim et al., 2014b; Kahrilas, Dodds, Dent, Logemann, & Shaker, 1988; Lang & Shaker, 2000; Sivarao & Goyal, 2000). At rest, constant presence of tone at the UES enables a functional barrier between pharynx and oesophagus. Manometrically, this barrier is identified as a zone of high pressure (Lang, 2013; S. Singh & Hamdy, 2005). During swallowing, the UES opens during hyolaryngeal excursion allowing for bolus transfer from the pharynx into the oesophagus (S. Singh & Hamdy, 2005). This review will specifically focus on anatomy, physiology, neural control, and behavioural manipulation of the UES. As hyolaryngeal excursion is relevant for UES opening, anatomy of the hyolaryngeal complex and its displacement during swallowing is further discussed in this Chapter.

### **4.1. Anatomy**

The UES encompasses the cricopharyngeus, the inferior pharyngeal constrictor, and muscle fibres of the cervical oesophagus (Lang, 2013; Nilsson, Isberg, & Schiratzki, 1989) (Figure 1). Based on data of a study casting the cross-sectional area (CSA) of the UES in a cadaveric sheep, it has been suggested that the UES may be kidney shaped while the oesophagus is round (Belafsky et al., 2013). In a study using high-frequency endoluminal sonography, the mean CSA of the UES at rest was  $0.87 \pm 0.33 \text{ cm}^2$  (L. S. Miller et al., 2004). The length of the high-pressure zone has been found to be age dependent with decreased length in elderly subjects (Samuel & Shaker, 2013). Hernandez and colleagues (2010) reported a length ranging between 3.0 and 4.5 cm with a median length of 4.0 cm. Further, it has been documented that the length of the UES high-pressure zone differs between the anterior and posterior portion of the UES. In older individuals, the length of the UES high-pressure zone was found to be  $1.9 \pm 0.1 \text{ cm}$  at the anterior portion and  $2.1 \pm 0.7 \text{ cm}$  at the posterior portion (Bardan et al., 2000). In young healthy individuals, an anterior length of the UES high-pressure zone of  $3.1 \pm 0.2 \text{ cm}$  and a posterior length of  $2.9 \pm 0.1 \text{ cm}$  was found (Bardan et al., 2000).



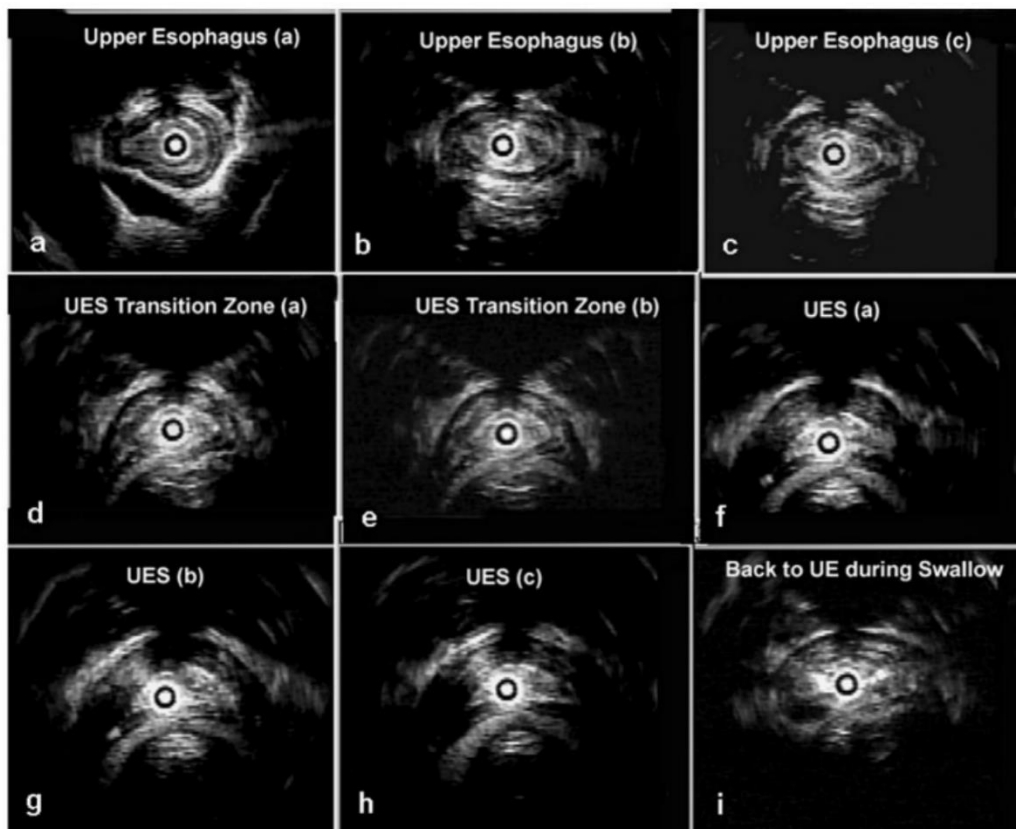
**Figure 1.** Posterior view of the inferior pharyngeal constrictor (IPC), cricopharyngeus (CP), and upper oesophagus (UE) (Mu & Sanders, 2007)<sup>3</sup>.

#### **4.1.1. Cricopharyngeus Muscle**

Antonio Maria Valsalva was the first to provide a detailed description of the cricopharyngeus as a distinct muscle in the early 18<sup>th</sup> century (Marchese-Ragona et al., 2014). The striated cricopharyngeus constitutes the most prominent part of the UES (Jungheim et al., 2014a; Nilsson et al., 1989; S. Singh & Hamdy, 2005). It forms an approximately 1 cm wide, c-shaped muscle band, originating from the lateral aspect of the cricoid cartilage, the membrane cricothyroidea (Jungheim, Janhsen, Miller, & Ptok, 2015; Kahrilas et al., 1988; Lang, 2013; L. S. Miller et al., 2004) (Figure 2). There are conflicting data regarding the vertical length of the cricopharyngeus. In a study using a high-frequency ultrasound miniprobe, the median length of the cricopharyngeus was found to range between 2.0 and 4.0 cm, with a median length of 3.5 cm (Hernandez et al., 2010). Yet, there are data to suggest a shorter length of approximately 0.7 cm (Ertekin & Aydogdu, 2002).

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<sup>3</sup> From "Neuromuscular specializations within human pharyngeal constrictor muscles" by Mu and Sanders (2007), *The Annals of Otolaryngology, Rhinology & Laryngology*, 116 (8), p. 606. Reprinted with permission of SAGE Publications.



**Figure 2.** Cross-sectional ultrasound images of the upper oesophageal sphincter (UES) and upper oesophagus in a healthy subject obtained using high-frequency endoluminal sonography. While the cross-sectional area (CSA) of the oesophagus is oval, the UES is c-shaped (L. S. Miller et al., 2004)<sup>4</sup>.

Within the cricopharyngeus, a superficial oblique oriented layer (pars obliqua) can be distinguished from a deeper, horizontally-oriented layer (pars fundiformis) (Jungheim et al., 2014a; Lang, 2013; Sivarao & Goyal, 2000). The pars obliqua laterally extends from the cricoid cartilage and inserts with the median pharyngeal raphe dorsally. The pars fundiformis forms a loop with no insertion into the pharyngeal raphe; caudally, the lower fibres obliquely deviate and border on the cranial oesophagus (Jungheim et al., 2014a; Lang, 2013; Lang & Shaker, 2000). The pars obliqua and pars fundiformis are composed of an inner and an outer layer of fibres. The inner layer is thicker, constituting two-thirds of the total thickness (Jungheim et al., 2014a). The dorsal area between the two pars, the Killian's dehiscence or Killian's triangle, is

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<sup>4</sup> From "Evaluation of the upper esophageal sphincter (UES) using simultaneous high-resolution endoluminal sonography (HRES) and manometry" by L. S. Miller et al. (2004), *Digestive Diseases and Sciences*, 49 (5), p. 706. Reprinted with permission of Springer Nature.

composed of fewer muscle fibres, thus it is predisposed for development of Zenker's diverticulum (Jungheim et al., 2014a).

The muscles fibre composition of the cricopharyngeus differs to other striated muscles. While striated muscles typically consist of parallel oriented muscle fibres, the cricopharyngeus is composed of a muscle network of small (25 - 35  $\mu\text{m}$ ), slowly contracting fibres (type 1) as well as fast contracting fibres (type 2) (Lang, 2013; S. Singh & Hamdy, 2005; Sivarao & Goyal, 2000). Unlike most of the surrounding muscles of the pharynx and larynx, predominantly slow contracting fibres have been identified in the cricopharyngeus (Brownlow, Whitmore, & Willan, 1989; Lang, 2013; Lang & Shaker, 2000; Mu & Sanders, 1998). Type 1 fibres constitute 69% of the pars obliqua, and 76% of the pars fundiformis (Jungheim et al., 2014a; Lang, 2013). Notably, the portion of elastic connective tissue in the cricopharyngeus is larger in comparison to most striated muscles (Ertekin & Aydogdu, 2002; Lang, 2013; S. Singh & Hamdy, 2005; Sivarao & Goyal, 2000). Connective tissue may contribute to the elasticity of the cricopharyngeus relevant for its function at rest and during swallowing. Maximum tension at the cricopharyngeus is reached at approximately 1.7 times the resting length while most striated muscles demonstrate maximal tension at resting length (Lang, 2013).

#### ***4.1.2. Inferior Pharyngeal Constrictor***

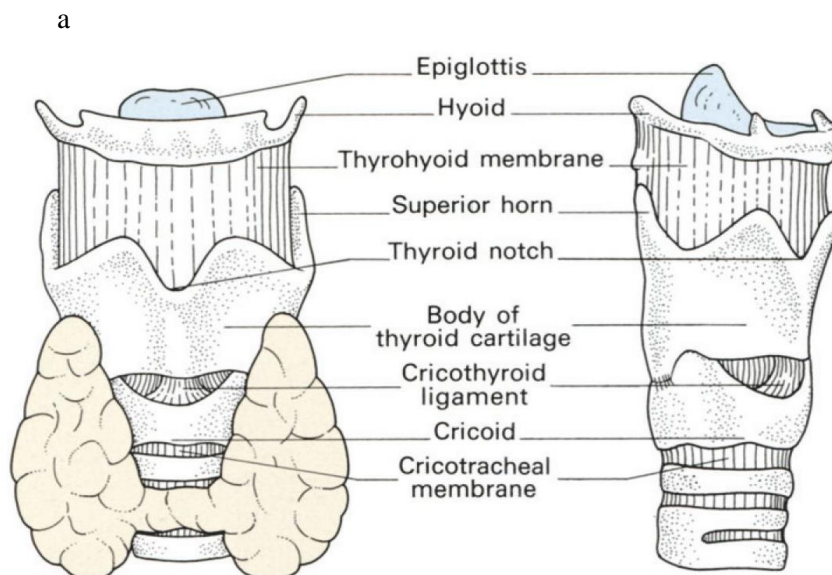
The fibres of the inferior pharyngeal constrictor originate laterally from the thyroid and cricoid cartilage and run dorsally, where they insert into the posterior pharyngeal midline raphe. Fast-twitch fibres have been found to be predominantly in the rostral portion of the inferior pharyngeal constrictor (61%) while the caudal region contains 30% fast-twitch fibres (Lang, 2013; Mu & Sanders, 2001). Similar to the cricopharyngeus, two fibre layers can be distinguished within the inferior pharyngeal constrictor. The superficial layer consists predominantly of fast contracting fibres, the deeper layer is mainly composed of slowly contracting fibres (Lang, 2013; Mu & Sanders, 1998). While in the caudal segment of the inferior pharyngeal constrictor the inner layer is twice as thick as the superficial layer, the opposite is true for the rostral portion of the inferior pharyngeal constrictor (Lang, 2013).

#### ***4.1.3. Cervical Oesophagus***

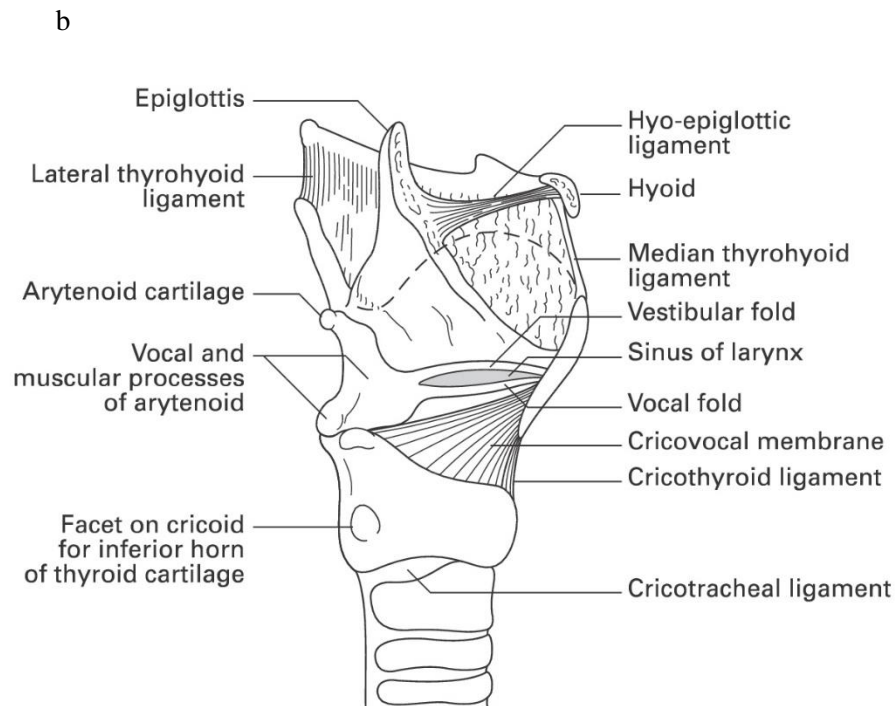
The cranial aspect of the oesophagus functionally contributes to the UES. The horizontally running striated muscle fibres are approximately the same size as the fibres of the cricopharyngeus (Lang, 2013). In animal studies, the fibres are predominantly fast twitch; however, the fibre type is not yet clearly established in humans (Lang, 2013).

#### 4.1.4. The Hyolaryngeal Complex

As stated previously, the cricopharyngeus is attached to the cricoid cartilage, an anatomical component of the hyolaryngeal complex (Figure 3). The hyolaryngeal complex is an interconnected group of structures, comprising the larynx, hyoid bone, various muscles, as well as membranes and ligaments (Fuller et al., 2012; Pearson et al., 2012; Pearson & Zumwalt, 2014). The larynx is composed of three unpaired cartilages (cricoid, thyroid, and epiglottis), three paired cartilages (arytenoids, cuneiforms, corniculates), as well as diverse membranes and ligaments. The larynx is inferior to the hyoid and superior to the trachea, extending approximately from the third to the sixth vertebra of the spinal cord. The hyoid is located above the larynx at the height of the third vertebra of the spinal cord. This bone is suspended through ligaments from the styloid processes with no direct connection to another bone and is primarily connected to the larynx via the thyrohyoid muscle and the hyothyroid membrane (Fuller et al., 2012; Lang, 2013). Diverse muscles attach to the hyoid, including the suprahyoid muscles that insert into the superior facet of the hyoid. The suprahyoid muscles comprise the bilateral digastric muscle (with an anterior and posterior belly), stylohyoid, mylohyoid, and geniohyoid (Daniels & Huckabee, 2014; Fuller et al., 2012; Jungheim et al., 2014a; Lang, 2013). Further, the infrahyoid muscles, including thyrohyoideus, sternohyoides, sternothyroideus, and omohyoides, insert into the lower aspect of the hyoid (Jungheim et al., 2014a; Lang, 2013).







**Figure 3.** Anatomy of the hyolaryngeal complex (Ellis & Mahadevan, 2013)<sup>5</sup>.

## 4.2. Physiology and Functions

### 4.2.1. At Rest

The contracted UES at rest builds a functional barrier between the pharynx and oesophagus (Lang, 2013; S. Singh & Hamdy, 2005). This barrier prevents potential refluxate from passing into the airway and extraneous air from entering into the oesophagus (Jungheim et al., 2014b; S. Singh & Hamdy, 2005). The lumen at the UES is occluded due to contraction of the UES muscles and passive forces of the elastic muscle properties (Lang, 2013). Further, it has been suggested that inelastic adjacent anatomical structures compress the UES from anteriorly and posteriorly (J. P. Meyer, Jones, Walczak, & McCulloch, 2016; A. J. Miller, 1999). Continuous muscle activity at the UES is electromyographically identified as constant presence of tone (Ertekin & Aydogdu, 2002). Notably, constant presence of tone at rest has been found mainly for the cricopharyngeus, while electromyographic (EMG) activity at the inferior pharyngeal constrictor is minimal (Halum, Shemirani, Merati, Jaradeh, & Toohill, 2006). Manometrically, the UES at rest is identified as a zone of high pressure. Jones, Hammer, Hoffman, and

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<sup>5</sup> From “Clinical anatomy: Applied anatomy for students and junior doctors” by Ellis and Mahadevan (2013), ebook 13<sup>th</sup> Ed., p. 312/314. Reprinted with permission of Wiley Books.

McCulloch (2014) reported a moderate positive correlation between UES resting pressure and cricopharyngeal EMG. In a study by L. S. Miller and colleagues (2004), UES resting pressure was compared between healthy volunteers ( $n = 7$ ) and human cadavers ( $n = 4$ ). It was revealed that active UES muscle tone was the biggest contributor to the peak UES pressure. Only approximately 26.5% of the pressure was due to factors such as elasticity.

There is some controversy regarding axial and radial asymmetry of the UES high-pressure zone (Bardan et al., 2000; Castell & Castell, 1993; Samuel & Shaker, 2013). J. P. Meyer and colleagues (2016) investigated radial pressure asymmetry in healthy subjects using a 3-D HRM system and a 4.2 mm catheter measuring circumferentially. The authors documented higher UES resting pressure in the anterior-posterior direction as compared to the lateral directions. Interestingly, in a study using a water-perfused system, Bardan and colleagues (2006) found that pressure asymmetry at the UES depends on the catheter size and catheter shape. Higher pressure in the anterior-posterior direction was found compared to lateral direction if using a large-sized (4.8 mm), round catheter. Using a flat catheter (width 4.8 mm, thickness 1.2 mm), that may better conform to the natural shape of the UES, symmetric pressure in anterior-posterior and lateral direction was found. The authors speculated that due to the configuration of the UES, the bigger round catheter applied stronger stretch on the sphincter in the anterior-posterior direction. Thus, increased pressure may be stretch-induced rather than reflective of true radial pressure asymmetry.

A manometry catheter in situ produces additional tension on the UES (Jungheim, Schubert, Miller, & Ptok, 2015). It seems likely that different catheter diameters may affect resting pressure differently. Thus, variability in reported UES resting pressure in healthy adults across studies that are using different catheters and manometry systems is not surprising. Using low-resolution manometry, Castell and Castell (1993) reported a mean UES resting pressure of  $73 \pm 29$  mmHg. Williams, Pal, Brasseur, and Cook (2001) found a mean maximum UES resting pressure of  $84 \pm 13$  mmHg in a study using a water-perfused HRM system and a 4.0 mm catheter. More recent studies used solid-state HRM systems in the evaluation of UES pressure. A median resting pressure, often referred to as basal pressure, of 49 mmHg (interquartile range (IQR) 40.3 – 55.8 mmHg) was documented by Pandolfino, Ghosh, Zhang, Han, and Kahrilas (2007) who utilised a 4.2 mm catheter. Differently, a median resting pressure  $> 70$  mmHg was reported by Silva and colleagues (2013) (76.3 mmHg, range 58.2 – 109.1 mmHg) and by Weijenborg, Kessing, Smout, and Bredenoord (2014) (72 mmHg). Unfortunately, the catheter size was not reported in the latter two studies. The impact of the catheter size on pressure values

is further highlighted by the normative data collected in 29 participants by Jungheim, Schubert, and colleagues (2015) using a solid-state HRM system with a 2 mm catheter. Considering the small catheter diameter, it is not surprising that the authors found the lowest mean resting pressure of  $42.5 \pm 18.7$  mmHg as compared to the studies detailed above. In addition to technical aspects including catheter, subject-related factors may also have an impact on UES resting pressure.

Previous research has explored the effect of sex and age on UES resting pressure. van Herwaarden and colleagues (2003) examined UES resting pressure in 45 men and 39 women using a solid-state low-resolution manometry system. Results revealed higher UES resting pressure in females compared to males. Notably, there is insufficient information provided regarding measurement method of resting pressure for the study to be replicated. The study findings contrast to results reported by Butler and colleagues (2009) who did not find a main effect of sex on UES resting pressure. Other than the effect of sex, the effect of age on UES resting pressure is also disputed in the literature. There are data to suggest that UES resting pressure is significantly lower in older healthy subjects compared to younger individuals (Bardan et al., 2000; van Herwaarden et al., 2003). However, no significant association between age and UES resting pressure was reported in other studies (Butler et al., 2009; D. W. Shaw et al., 1995; Yoon, Park, Park, & Jung, 2014). The findings of the aforementioned studies indicate that there is a discrepancy in the literature regarding the contribution of age and sex to the between-subject variability of UES resting pressure.

Since age and sex inconsistently account for between-subject variability of UES resting pressure, further factors that may contribute to the high between-subject (Kahrilas et al., 1987; Rezende, Herbella, Silva, Panocchia-Neto, & Patti, 2014) and within-subject variability of UES resting pressure need to be considered (Rezende et al., 2014). Both within- and across-subject variability is highlighted in a study by Rezende and colleagues (2014) who measured UES resting pressure in 36 healthy subjects using HRM at the beginning and at the end of an examination. The examination lasted, on average, eight minutes. UES resting pressure was significantly higher at the beginning of the session with a mean of  $100.6 \pm 45.6$  mmHg (range between 22.0 and 201.1 mmHg) as compared to data collected at the completion of the examination ( $70.7 \pm 31.2$  mmHg, range 23 - 147.3 mmHg). While the change in pressure over time indicates intra-individual variability, between-subject variability is indicated by the large range of pressure values at the two analysed time points.

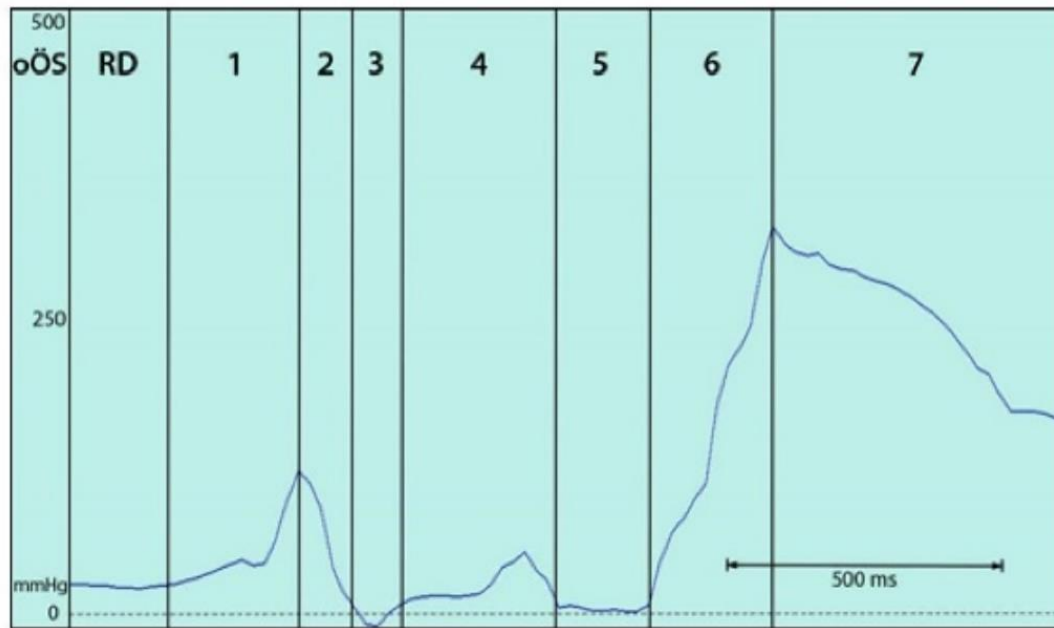
Further variables that may contribute to intra-subject variability of UES resting pressure in healthy subjects have been documented in the literature. An increase of UES resting pressure was documented in a study by Cook, Dent, Shannon, and Collins (1987), who evaluated the effect of acute stress on UES resting pressure. Participants ( $n = 13$ ) were exposed to diverse stressors, such as time pressure during performance of a dichotic listening task. Stress was confirmed by increased heart rate and blood pressure. Results indicated that acute stress may significantly increase UES resting pressure. Further research suggested an association of inspiration and phonation and increased UES resting pressure. Kahrilas and colleagues (1987) assessed UES pressure in healthy subjects at rest ( $n = 8$ ) and found increased pressure with inspiration during rest and sleep. This finding was confirmed by Eastwood, Katagiri, Shepherd, and Hillman (2007) who studied UES resting pressure in 10 healthy subjects and reported significantly higher UES pressure values at the end of inspiration compared to expiration, independent of whether the subjects were awake or asleep. Perera and colleagues (2008) analysed UES resting pressure during sustained phonation of high and low pitch vowels in healthy subjects ( $n = 17$ ). There was a significant increase in UES resting pressure during phonation, independent of pitch. Further, DiRe, Shi, Manka, and Kahrilas (2001) assessed UES pressure at rest in eight subjects over 30 minutes and found higher pressure during periods of frequent swallowing. Yet, it was not specified whether pressure data before and after a swallow were excluded from analysis and no quantification of frequent swallowing was provided. Further, there are studies reporting on aspects relating to a resting pressure decrease. Kahrilas and colleagues (1987) found lower UES resting pressure in healthy subjects ( $n = 8$ ) during sleep. This finding was confirmed by Eastwood and colleagues (2007). Vanner, Pryle, O'Dwyer, and Reynolds (1992) reported decreased UES resting pressure in patients after intravenous application of anaesthesia.

Further, there is evidence that body posture impacts UES resting pressure. Takasaki, Umeki, Kumagami, and Takahashi (2010) studied the effect of head rotation on UES pressures in 18 healthy subjects. An endoscope was used to see whether the catheter in situ passed the UES on the subjects left or right side. Higher UES resting pressure values were found if participants turned their head towards the catheter as compared to a neutral head position. Conversely, lower pressure values were found if the head was turned away from the catheter. Notably, it is indicated that UES pressure was assessed based on a single sensor located “above the cricopharyngeus muscle” (p. 215). Thus, it is questionable whether the results truly represent UES resting pressure or are a measure of distal pharyngeal pressure.

Altered UES resting pressure has further been reported as a result of several UES reflexes, including the pharyngo-UES contractile reflex, the oesophago-UES contractile reflex, or the oesophago-UES relaxation reflex (Lang, 2013). The pharyngo-UES reflex was investigated in 10 healthy subjects by Shaker and colleagues (1997) who found significantly increased UES resting pressure following pharyngeal water injection, independent of the water temperature. In a study by Babaei and colleagues (2012), the effect of oesophageal stimulation on UES pressure was studied. This study revealed that air injection into the oesophagus resulted frequently in a UES relaxation response. Conversely, water injection was associated with a contraction reaction of the UES. Szczesniak, Fuentealba, Burnett, and Cook (2008) explored UES reflexes on oesophageal stimulation in 55 healthy subjects. The authors reported that oesophageal distension using a balloon resulted in a UES contraction response in the majority of participants. Differently, air injection into the oesophagus caused either UES relaxation or contraction.

#### ***4.2.2. UES Function During Swallowing***

Successful bolus passage through the UES requires a precise interaction between relaxation of the cricopharyngeus, traction forces of the hyolaryngeal complex acting on the UES to elicit opening, and bolus propulsion (Easterling & Shaker, 2013; Jungheim et al., 2014b; Lang & Shaker, 2000). Distensibility of the UES muscles is a further prerequisite of successful UES function during swallowing (Easterling & Shaker, 2013). Differentiation of five phases of UES opening during swallowing was suggested by Jacob and colleagues (1989) based on a concurrent videofluoroscopic and manometric study in eight healthy subjects. The proposed phases included relaxation (1), opening (2), distention (3), collapse (4), and closure (5). These five phases were confirmed in a study using HRM by S. Meyer, Jungheim, and Ptak (2012); yet, the authors proposed an additional phase at the very beginning to reflect an observed pressure increase prior to pressure relaxation. Later, Jungheim and colleagues (2014b) suggested adding a restitution phase following UES closure. This phase reflects the period during which increased pressure at the UES, as observed during closure, drops back to pre-swallow resting pressure. The expanded classification by Jungheim and colleagues (2014b) will be used for review of UES function during swallowing (Figure 4).



**Figure 4.** Illustration of the pressure tracings of a sensor at the upper oesophageal sphincter (UES) depicting the seven phases of UES opening during swallowing according to the classification of Jungheim and colleagues (2014b)<sup>6</sup>.

*Phase 1* describes an initial pressure rise during elevation of the hyolaryngeal complex (S. Meyer et al., 2012) as observed and reported in numerous studies using HRM (Geng, Hoffman, Jones, McCulloch, & Jiang, 2013; McCulloch, Hoffman, & Ciucci, 2010; Mielens, Hoffman, Ciucci, Jiang, & McCulloch, 2011; Ryu, Park, Oh, Lee, & Kang, 2016). This rise in pressure is likely related to activity of the UES muscles (Jungheim et al., 2014b). Using EMG, a burst of increased EMG activity was frequently measured at the cricopharyngeus immediately before the pause of EMG activity during swallowing; the reason for this muscle activity remains unclear (Ertekin & Aydogdu, 2002, 2003; Ertekin et al., 1995). One would question if this has to do with the slight initial pull from hyolaryngeal excursion resulting in a resistance reaction of the UES to opening until the cricopharyngeus receives neural signal to relax.

*Phase 2* commences with the start of relaxation. Cricopharyngeal relaxation can be identified manometrically by a decrease in pressure at the UES toward 0 mmHg (Jacob et al., 1989; S.

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<sup>6</sup> From “Physiologie des oberen Ösophagussphinkters” by Jungheim et al. (2014b), HNO, 62 (6), p. 463. Reprinted with permission of Springer Nature.

Meyer et al., 2012; S. Singh & Hamdy, 2005; Sivarao & Goyal, 2000). The drop of pressure occurs directly after the onset of swallowing, before the radiologically defined opening of the sphincter (Cook et al., 1989) while the larynx moves in superior and anterior direction (Cook et al., 1989; Sivarao & Goyal, 2000). Relaxation is considered a consequence of paused tonic activity of the cricopharyngeus (Cook et al., 1989; Ertekin & Aydogdu, 2002, 2003); yet, the exact underlying mechanisms of relaxation are not fully understood (Cook et al., 1989; S. Singh & Hamdy, 2005; Sivarao & Goyal, 2000). There is research documenting the relationship between pressure relaxation and muscle activity of the cricopharyngeus. Cook (1993) found an association between cessation of EMG activity of the cricopharyngeus and manometrically assessed relaxation. In a more recent study, a high correlation between duration of UES relaxation and deactivation of cricopharyngeal EMG activity was documented (Cock, Jones, Hammer, Omari, & McCulloch, 2016).

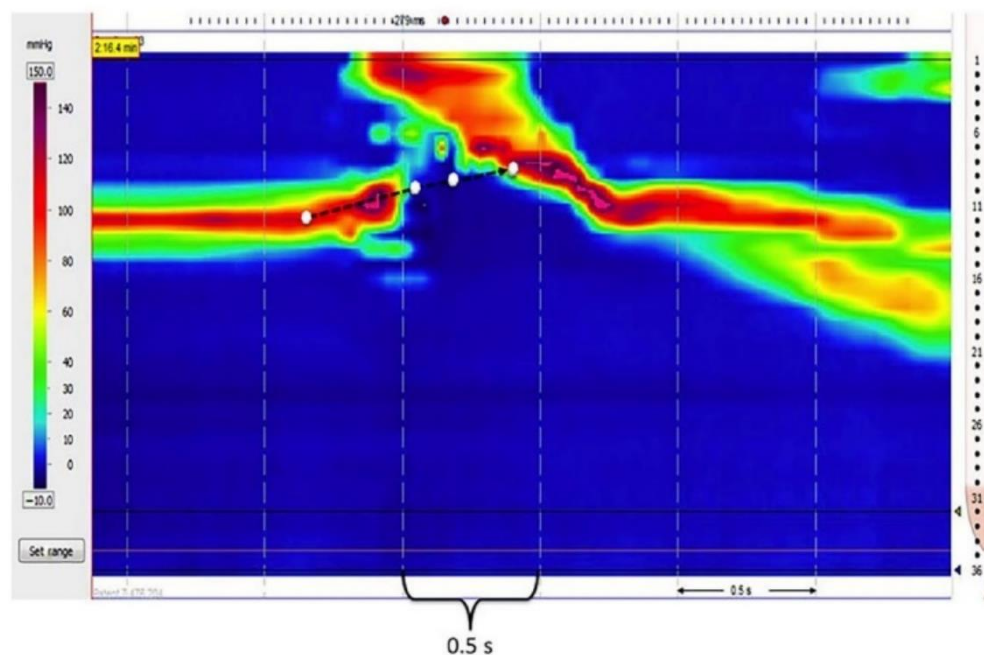
The relaxation phase lasts for approximately 0.5 s (Lang & Shaker, 2000). For example, Kahrilas and colleagues (1988) reported a mean relaxation duration of 0.37 s for dry swallows and 0.65 s for 20 mL liquid boluses. There are conflicting data in the literature whether the duration of pressure relaxation is affected by the bolus volume. Cook and colleagues (1989) reported no significant difference in duration of UES relaxation across different bolus volumes. Conversely, an increase in relaxation duration associated with larger volumes was documented in other studies (Butler et al., 2009; Cock, Jones, et al., 2016; Kahrilas et al., 1988). Interestingly, in the study by Cock and colleagues (2016), not only an increased duration of relaxation but also of cessation of cricopharyngeal EMG, was found for larger bolus volumes. Yoon and colleagues (2014) reported no significant difference in UES relaxation duration for different viscosities, namely water, barium, and yoghurt. Other than the effect of volume and viscosity, the effect of sex and age on UES relaxation duration has been explored. van Herwaarden and colleagues (2003) found longer relaxation during water swallows in healthy women than in men. Further, the authors found an age effect on the duration of UES relaxation with shorter durations in elderly participants during swallows of water and solids. Conversely, Yokoyama, Mitomi, Tetsuka, Tayama, and Niimi (2000) did not detect an effect of age on UES relaxation duration in 56 healthy subjects who underwent manofluorographic procedure. Regarding the degree of relaxation, no difference in nadir pressure during relaxation between older and younger healthy subjects was found in study by D. W. Shaw and colleagues (1995). In contrast, Butler and colleagues (2009) reported that older, healthy adults (n = 21) showed decreased relaxation during saliva swallowing compared to younger subjects (n = 23).

*Phase 3* delineates the opening of the UES during swallowing. Opening of the UES has been found to be associated with displacement of the hyolaryngeal complex during swallowing (Jacob et al., 1989; Lang, 2013). There are studies suggesting that the anterior movement of the hyolaryngeal complex principally contributes to UES opening. For example, Cook and colleagues (1989) found that the UES opened shortly after the initiation of anterior hyolaryngeal movement. Other studies highlighted that anterior hyoid excursion is the main biomechanical event contributing to UES opening. Jacob and colleagues (1989) documented a higher temporal correlation between UES opening duration and anterior rather than superior hyoid movement. Similarly, a study by R. Ishida, Palmer, and Hiiemae (2002) reported that the time of bolus entering the UES occurred closer to the onset of anterior hyoid movement than the onset of superior hyoid displacement. Lastly, Nakane, Tohara, Ouchi, Goto, and Uematsu (2006) reported that UES opening width correlated positively with anterior hyoid movement but negatively with superior hyoid excursion.

During hyolaryngeal displacement, the relaxed UES is passively stretched and opening is elicited (Ertekin & Aydogdu, 2003; Jungheim et al., 2014b; Sivarao & Goyal, 2000). Negative pressure values may be reached with the beginning of UES opening during hyolaryngeal excursion (Samuel & Shaker, 2013; Williams et al., 2001). As the sphincter fully opens, pressure returns to 0 mmHg (Jacob et al., 1989; Jungheim et al., 2014b; S. Meyer et al., 2012). With the excursion of the hyolaryngeal complex during swallowing, the UES moves superiorly (Kahrilas et al., 1988; S. Singh & Hamdy, 2005); the extent of the superior UES movement was found to increase with larger bolus volume (Kahrilas et al., 1988). On HRM contour plot, a shift of the UES pressure band in superior direction reflects the movement of the catheter in relation to the UES movement during laryngeal excursion (Williams et al., 2001) (Figure 5).

Duration of UES opening has been quantified in numerous studies. Molfenter and Steele (2012) reviewed 20 studies documenting UES opening duration across different bolus volumes, based on videofluoroscopic analysis. In this literature review, a small range of mean duration, from 0.21 – 0.67 s, was found. While the review only included studies using videofluoroscopy, there is a study using a 320-row area detector computed tomography (CT) to assess UES opening duration. In this study, the opening duration for 3, 10, and 20 mL honey-thick liquid boluses were 0.508 s, 0.562 s, 0.600 s, respectively (Shibata et al., 2017). Bolus volume has been found to impact UES opening duration with prolonged opening for increased size of the bolus (Cock, Jones, et al., 2016; Jacob et al., 1989; Kahrilas et al., 1988; Kern et al., 1999; Molfenter & Steele, 2012; Rademaker, Pauloski, Colangelo, & Logemann, 1998; Shibata et al., 2017).





**Figure 5.** High-resolution manometry (HRM) contour plot depicting the movement of the upper oesophageal sphincter (UES) during swallowing. Based on manometric and videofluoroscopic data, the location of the centre of the UES (white circle) is shown at baseline, during UES opening, at maximum laryngeal elevation, and during UES closure (Nativ-Zeltzer, Logemann, Zecker, & Kahrilas, 2016)<sup>7</sup>.

Further, there are data to suggest that bolus viscosity may impact UES opening duration (Dantas et al., 1990; Kendall, Leonard, & McKenzie, 2001; Lazarus et al., 1993). An effect of age on UES opening duration has been documented with longer opening duration in older subjects (Kendall & Leonard, 2002; Molfenter & Steele, 2012; Rademaker et al., 1998; Robbins, Hamilton, Lof, & Kempster, 1992). In a study by Robbins and colleagues (1992), UES opening was evaluated in 40 healthy females and 40 healthy males using videofluoroscopy. This study further revealed an effect of sex on UES opening duration with females showing longer durations than men (mean 0.49 s, 0.43 s, respectively).

Factors that may affect extent of UES opening have been reported in the literature. Increased UES opening diameter has been documented for larger boluses (Cook et al., 1989; Jacob et al., 1989; Kahrilas et al., 1988; D. W. Shaw et al., 1995). An effect of age on the extent of UES

<sup>7</sup> From “Pressure topography metrics for high-resolution pharyngeal-esophageal manofluorography—a normative study of younger and older adults” by Nativ-Zeltzer et al. (2016), *Neurogastroenterology & Motility*, 28(5), p. 727. Reprinted with permission of John Wiley and Sons.

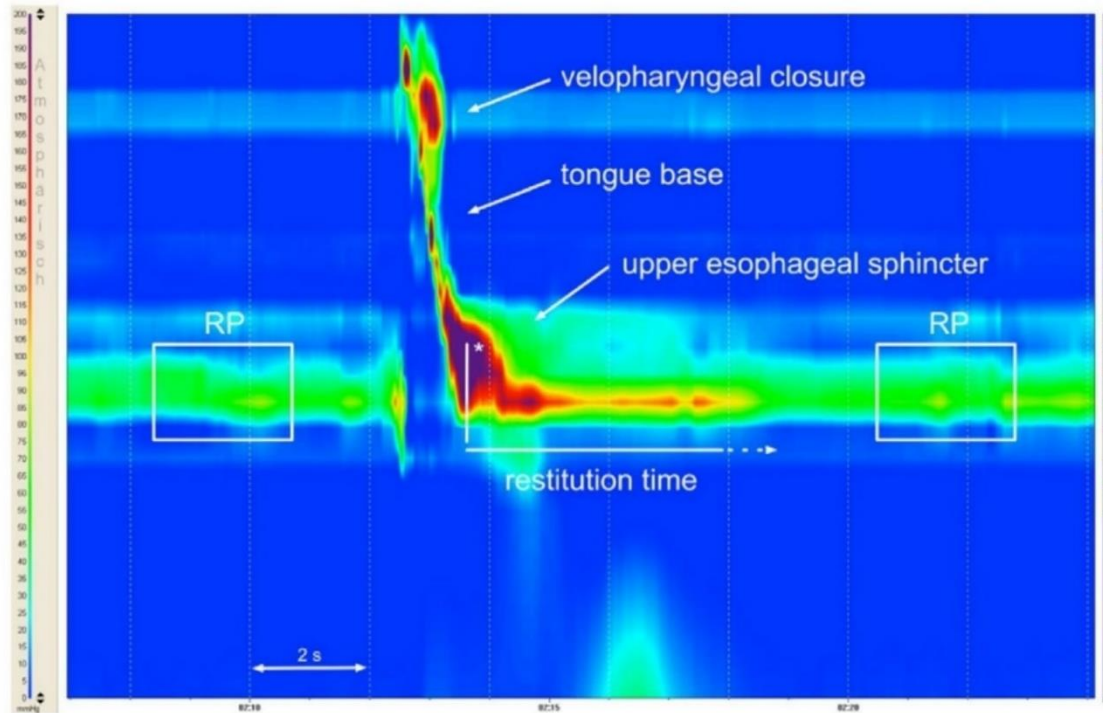
opening has been documented by D. W. Shaw and colleagues (1995), who found smaller transverse opening diameter in older subjects. This finding was supported by Kern and colleagues (1999), yet, smaller anteroposterior UES opening diameter was only found to be statistically significant for barium boluses of volume 5 mL and not for 10 mL.

*Phase 4* encompasses intra-swallow distention and bolus passage through the UES. During bolus passage through the sphincter, an increased stretch of the UES muscles occurs (Jungheim et al., 2014b). Increased intrabolus pressure during bolus passage contributes to UES opening. This pressure is generated by the base of the tongue as well as by the upper and middle pharyngeal constrictors (Jacob et al., 1989; S. Meyer et al., 2012; S. Singh & Hamdy, 2005) with greater intra-bolus pressure for larger bolus volumes (D. W. Shaw et al., 1995). An effect of age on the amplitude of intrabolus pressure has been documented by D. W. Shaw and colleagues (1995) with higher intrabolus pressure in older healthy subjects compared to younger adults.

In *Phase 5*, the bolus has passed through the UES. Thus, this phase describes the decline in distention of the UES muscles after bolus passage (Jacob et al., 1989). Due to this, pressure returns from elevated intra-bolus pressure to 0 mmHg; the UES is not tonically contracted yet (Jungheim et al., 2014b; S. Meyer et al., 2012).

*Phase 6* characterises the contraction of the sphincter muscles and closure of the lumen after bolus passage (Jacob et al., 1989), while the hyolaryngeal complex returns to resting position (Cook et al., 1989; Sivarao & Goyal, 2000). Following the pause of cricopharyngeal EMG activity during UES opening, a burst of increased EMG activity was observed (Ertekin & Aydogdu, 2002; Ertekin et al., 1995). In this phase, pressure at the UES exceeds resting pressure values (Kahrilas et al., 1988; Pal, Williams, Cook, & Brasseur, 2003); elevated pressure may minimise the risk of regurgitation (Jungheim et al., 2014b).

*Phase 7*, the stage of restitution, describes the period during which elevated pressure at the UES slowly drops until pre-swallow resting pressure is reached (S. Meyer et al., 2012) (Figure 6). This phase may last 9 to 11 s (Jungheim et al., 2016).



**Figure 6.** High-resolution manometry (HRM) contour plot depicting resting pressure (RP) pre-swallow, restitution time, and resting pressure post-swallow (Jungheim et al., 2016)<sup>8</sup>.

#### 4.2.3. Hyolaryngeal Excursion

As stated previously, UES opening occurs during hyolaryngeal excursion. There are data to suggest that UES opening mainly relates to anterior hyoid movement (R. Ishida et al., 2002; Jacob et al., 1989). Yet, movement of the hyoid and larynx are not separable as the two structures are connected (Dodds et al., 1990; Fuller et al., 2012; Kendall, 2008). Thus, hyolaryngeal displacement, rather than only hyoid excursion, will be reviewed in this section.

The upward and forward movement of the hyoid is attained by contraction of the suprahyoid muscles, by which the hyoid is connected with the mandible and skull (Dodds et al., 1990; Fuller et al., 2012). Contraction of the anterior belly of the digastric, mylohyoid, geniohyoid, posterior belly of the digastric, and stylohyoid pull the hyoid superiorly. While the posterior belly of the digastric, stylohyoid, and middle pharyngeal constrictors pull the hyoid in superior

<sup>8</sup> From “Calculation of upper esophageal sphincter restitution time from high resolution manometry data using machine learning” by Jungheim et al. (2016), *Physiology & Behavior*, 165, p. 414. Reprinted with permission of Elsevier.

and posterior direction, the geniohyoid is mainly responsible for the anterior displacement of the hyoid (Fuller et al., 2012). The importance of the suprahyoid muscles for elevating and moving the hyoid anteriorly is generally recognised; however, individual contributions of isolated muscles are not yet fully understood (Okada et al., 2013; Pearson, Langmore, & Zumwalt, 2011). In a study by Pearson and colleagues (2011), the geniohyoid and mylohyoid were found to have the greatest structural potential among the suprahyoid muscles for hyoid displacement in anterior and superior direction, respectively. However, structural analysis is limited in its value, as structural potential does not necessarily relate to functional significance (Pearson et al., 2011). The impact of different factors on intra-swallow hyoid movement has been studied, including sex (R. Ishida et al., 2002; Y. Kim & McCullough, 2008; Leonard, Kendall, McKenzie, Gonçalves, & Walker, 2000), age (Y. Kim & McCullough, 2008; D. W. Shaw et al., 1995), bolus size (Cook et al., 1989; Dodds et al., 1988; Jacob et al., 1989; Leonard et al., 2000), consistency (R. Ishida et al., 2002), and number of swallows (R. Ishida et al., 2002).

The larynx is approximated to the hyoid during swallowing by contraction of the paired thyrohyoid. Thus, thyrohyoid approximation contributes to superior movement of the UES (S. Singh & Hamdy, 2005). The thyrohyoid belongs with the sternohyoid, and omohyoid to the group of infrahyoid muscles (Easterling & Shaker, 2013; Jungheim et al., 2014b; Lang, 2013; Lang & Shaker, 2000; Ludlow, 2005). The sternohyoid and omohyoid muscles are relaxed during hyolaryngeal displacement to enable maximal elevation (Jungheim et al., 2014b). The effect of factors including sex and bolus size has been documented in the literature (Leonard et al., 2000).

In addition to the supra- and infrahyoid muscles, the potential contribution of the longitudinal pharyngeal muscles, including stylopharyngeus, palatopharyngeus, and salpingopharyngeus, in hyolaryngeal complex displacement is discussed and supported by existing research (Pearson, Hindson, et al., 2013; Pearson et al., 2012; Pearson & Zumwalt, 2014). These muscles primarily elevate the pharyngeal wall, and potentially assist in elevating the hyolaryngeal complex (Jungheim et al., 2014a; Lang, 2013; Lang & Shaker, 2000; Pearson et al., 2012).

#### **4.3. Neural Control of UES Musculature**

Peripheral motor innervation of the human UES is not yet fully understood and contradictory data are reported in the literature (Ertekin & Aydogdu, 2002; Mu & Sanders, 1996, 1998). One

reason for the controversy is that earlier data were derived from animal studies. However, the cricopharyngeus in some animals differs significantly from the human cricopharyngeus (Mu & Sanders, 1996; Sasaki et al., 1999). While the cricopharyngeus is composed of two muscle layers (pars fundiformis, pars obliqua) in humans, not all animals demonstrate this feature (Lang & Shaker, 2000). Thus, data from animal studies can only be applied to humans with limitations (Jungheim et al., 2014b; Lang & Shaker, 2000; Mu & Sanders, 1996). Furthermore, investigation of the nerves supplying the human UES is challenging, as branches of different nerves build a complex network (Mu & Sanders, 1996; Sasaki et al., 1999) and data interpretation of studies using EMG is limited due to muscles adjacent and overlying the cricopharyngeus (S. Singh & Hamdy, 2005). Despite challenges to evaluate peripheral control of the UES, there are data to suggest that the motor innervation of the cricopharyngeus, the inferior pharyngeal constrictor, and the cervical oesophagus differ (Mu & Sanders, 1996, 1998).

There are data to propose that fibres from the pharyngeal plexus supply the human cricopharyngeus (Mu & Sanders, 1996, 1998; Sasaki et al., 1999). However, Brok and colleagues (1999) postulated that the pharyngeal plexus is involved in control of the cricopharyngeus in some subjects only. Using a Sihler's staining technique, connections between the pharyngeal plexus and the laryngeal recurrent nerve were found in the region of the UES (Mu & Sanders, 1996, 1998), indicating potential contribution of the recurrent nerve in neural control of the UES. This finding aligns with data from EMG studies that identified branches of the recurrent nerve in the innervation of the cricopharyngeus (Brok et al., 1999; Sasaki et al., 1999). Using EMG intraoperatively in patients, Uludag and colleagues (2017) identified potential contribution of the pharyngeal plexus, recurrent laryngeal nerve, and the external branch of the superior laryngeal nerve in the innervation of the cricopharyngeus. While the pharyngeal plexus was found to supply the cricopharyngeus in all studied subjects, stimulation of the recurrent laryngeal nerve and the external branch of the superior laryngeal nerve resulted in muscle contraction in most trials, but, importantly, not all.

The inferior pharyngeal constrictor is supplied by nerve fibres of pharyngeal plexus (Brok et al., 1999; Mu & Sanders, 1996, 1998). Yet, as the pharyngeal plexus is a complex network of different nerves, it is difficult to determine exactly which fibres are involved in the innervation of the inferior pharyngeal constrictor (Jungheim et al., 2014a; Lang, 2013; Lang & Shaker, 2000; Mu & Sanders, 1996). More specifically, caudal branches of the pharyngeal branch of CN X (Mu & Sanders, 2001) and the recurrent laryngeal nerve of CN X (Brok et al., 1999)

were identified in the innervation of the inferior pharyngeal constrictor. The muscle fibres of the cervical oesophagus adjacent to the cricopharyngeus are innervated by the laryngeal recurrent nerve (Jungheim et al., 2014a; Lang, 2013; Lang & Shaker, 2000; Mu & Sanders, 1996, 1998).

Sensory innervation of the UES has primarily been studied in animals (Jungheim et al., 2014a). The glossopharyngeal, vagus, and superior laryngeal nerve (a branch of the vagus nerve) potentially carry sensory information from the human UES. However, the exact role which each nerve plays in neural control of the UES is not yet clear (Jungheim et al., 2014a; Lang & Shaker, 2000; S. Singh & Hamdy, 2005).

Data regarding central control mechanisms of the UES are mainly based on animal studies. These studies suggest involvement of sensory neurons in the nucleus tractus solitarius (Lang & Shaker, 1997) and motor neurons around and in the nucleus ambiguus (Lang, 2013; Lang & Shaker, 1997; A. J. Miller, 1999) in the central control of the UES. Other than the brainstem, supratentorial structures (Ertekin et al., 2001), including the anterior insula, the premotor cortex, and the precentral motor cortex, may be involved in the motor control the cricopharyngeus (Ertekin & Aydogdu, 2002). Ertekin and colleagues (2001) studied the responses of the cricopharyngeus to transcranial brain stimulation. In healthy subjects, motor evoked potentials were induced during stimulation of the motor cortex at the cranial midline vertex electrode position. The role of subcortical structures, including the cerebellum and basal ganglia, in the control of the UES have not been elucidated (Ertekin & Aydogdu, 2002).

#### **4.4. Behavioural Modulation**

UES opening during swallowing is embedded into the stereotypic sequence of events that constitutes pharyngeal swallowing (Ertekin & Aydogdu, 2003). Considering cortical structures involved in neural control of pharyngeal swallowing (Daniels & Huckabee, 2014), it is not surprising that there is evidence in the literature for volitional manipulation of UES opening. Swallowing techniques that have been documented to impact UES function include the Mendelsohn manoeuvre (Hoffman et al., 2012; Kahrilas et al., 1991) and effortful swallowing (Hiss & Huckabee, 2005; Hoffman et al., 2012).

Evaluation of these swallowing techniques in healthy subjects has allowed for edification of the capacity for behavioural manipulation without the confound of neural damage or reorganisation following events such as stroke. The Mendelsohn manoeuvre involves volitional

prolongation of laryngeal excursion during swallowing to increase UES opening duration and opening diameter (Logemann, 1998; Logemann & Kahrilas, 1990). An effect of this technique on UES opening duration in healthy subjects has been reported by Kahrilas and colleagues (1991) in a study using videofluoroscopy. Similarly, Hoffman and colleagues (2012) found a prolonged duration of nadir UES pressure based on a study using HRM. Conversely, other studies failed to detect an effect on UES opening or relaxation duration based on UES assessment using HRIM (Doeltgen et al., 2017), 320-row area detector CT (Inamoto et al., 2018), or videomanometry (Bodén et al., 2006). Further, there is lacking evidence of an effect of this technique on UES opening diameter in healthy subjects (Inamoto et al., 2018; Kahrilas et al., 1991). While the Mendelsohn manoeuvre was designed to behaviourally modulate UES opening, other aspects of UES function have been found to be altered in healthy subjects during execution of this technique. Such aspects include decreased maximum pre-opening UES pressure (Hoffman et al., 2012), decreased post-swallow maximum pressure at the UES (Bodén et al., 2006), and faster maximal opening of the UES (Doeltgen et al., 2017). Notably, other aspects of pharyngeal swallowing, apart from prolonged hyolaryngeal excursion and altered UES function, have been documented to change as an effect of this technique. Such alterations include pressure changes in the velopharynx (Hoffman et al., 2012), pharynx (Bodén et al., 2006; Doeltgen et al., 2017; Hoffman et al., 2012), and proximal oesophagus (Doeltgen et al., 2017). O'Rourke and colleagues (2014) found an increase of oesophageal non-peristaltic liquid swallows during performance of Mendelsohn manoeuvre as compared to normal swallows.

Effortful swallowing was originally designed to augment bolus clearance by increasing tongue movement toward the pharyngeal wall (Logemann, 1998; Poudoux & Kahrilas, 1995). This technique has been shown to change pressure in the oral cavity (Hind et al., 2001), velopharynx (Hoffman et al., 2012; Takasaki, Umeki, Hara, Kumagami, & Takahashi, 2011), and the pharynx (Hiss & Huckabee, 2005; Huckabee et al., 2005; Takasaki et al., 2011; Witte et al., 2008). Further, changes in hyolaryngeal excursion during effortful swallowing have been reported (Bülow et al., 1999; Hind et al., 2001). Additionally, there are studies documenting an effect of effortful swallowing on UES function in healthy subjects. Such effects include decreased nadir pressure (Witte et al., 2008), prolonged duration of intra-swallow relaxation (Hiss & Huckabee, 2005), increased nadir UES pressure duration (Hoffman et al., 2012), and increased UES opening duration (Hind et al., 2001). Hind and colleagues (2001) further assessed the effect of effortful swallowing on maximal UES opening diameter but found no change in diameter during execution of this technique.

While both the Mendelsohn manoeuvre and effortful swallowing have the potential to volitionally modulate UES function, opening is not directly manipulated. Rather, opening is indirectly elicited via biomechanical or pressure alterations of pharyngeal swallowing. There are no studies to date that report the potential for direct manipulation of UES function. Increased understanding of the potential of healthy and dysphagic subjects to directly modulate UES function during swallowing is critical for development of specific behavioural treatment options for UES dysfunction. Behavioural treatment options for UES impairment are limited. Invasive methods including muscle dilation, injection of botulinum into the cricopharyngeus, and myotomy are particularly common in patients with failed pressure relaxation. These patients may not benefit from behavioural techniques, such as the Mendelsohn manoeuvre, as it targets hyolaryngeal excursion rather than pressure relaxation. However, invasive interventions entail the risk of complications. Therefore, data about manipulation of the UES in healthy subjects may provide a foundation for potential behavioural treatment options for patients with impaired UES relaxation.



## **5. Instrumental Assessment of the UES**

In the clinical assessment of swallowing, limited direct evidence of UES function may be gained during the patient interview, CN examination, or clinical observation. A patient reporting that food gets stuck in the lower throat may call a clinician's attention to possible UES impairment (Logemann, 1998). There are subjective palpation methods, such as the four-finger method, to assess intra-swallow laryngeal displacement that contributes to UES opening (Logemann, 1998). However, there are concerns regarding reliability and accuracy of such methods; thus, caution is warranted when judging adequacy of hyolaryngeal excursion clinically (Brates, Molfenter, & Thibeault, 2018; McCullough et al., 2000). Indirect information about the integrity of swallowing physiology may be gained from interpretation of the CN examination. Clinical testing of jaw opening against resistance may indicate impaired anterior movement of the hyoid due to damage of CN V. Further, weak volitional cough or reduced voice quality may suggest impairment of CN X that innervates the UES (Daniels & Huckabee, 2014). Clinical assessment of oral intake may further provide subjective information about UES function. Altered quality of voice or expectoration of food post-swallow may result from residue in the pharynx. Yet, it remains unknown whether residue arises from reduced UES opening or from other pathophysiology, such as weak pharyngeal motility (Daniels & Huckabee, 2014; Logemann, 1998). While the information obtained during clinical swallowing assessment is of value, the additional use of instrumentation is required to gain insight into the adequacy of UES physiology. Precise diagnostics, including differentiation between UES compliance, poor hyolaryngeal movement, or insufficient pharyngeal pressure generation for bolus propulsion through the UES (Logemann, 1998), are paramount for specificity in rehabilitation (Daniels & Huckabee, 2014; Knigge, Thibeault, & McCulloch, 2014; Omari et al., 2015).

The use of different modalities for comprehensive assessment of UES function has been reported (Ahuja & Chan, 2016). For dynamic visualisation of UES opening and hyolaryngeal excursion, videofluoroscopy is the most commonly used modality in clinical and research arenas (Kendall, McKenzie, Leonard, Gonçalves, & Walker, 2000; Leonard et al., 2000). Further, the use of ultrasound (Chi-Fishman & Sonies, 2002b; Moriniere et al., 2013), MRI (Pearson & Zumwalt, 2014; Vijay Kumar, Shankar, & Santosham, 2013), and 320-row area detector CT (Inamoto et al., 2011; Inamoto et al., 2018) have been reported for this purpose. Fiberoptic endoscopic evaluation of swallowing plays a minor role in the evaluation of the UES as assessment of physiology is limited due to difficulties with visualisation (Ahuja & Chan,

2016). While these technologies visualise aspects of swallowing, there are techniques providing pressure data. This is of particular importance when differentially diagnosing UES noncompliance as failure of the UES to relax, which cannot be determined by observation of biomechanics alone.

Modalities for assessment of pressure at the UES include low-resolution manometry (Castell & Castell, 1993; Hiss & Huckabee, 2005), HRM (Jones, Hammer, et al., 2014; T. H. Lee, Lee, Hong, Lee, Jeon, Kim, Kim, Cho, Kim, Cho, Park, et al., 2014), and HRIM for combined pressure-flow analysis (Cock & Omari, 2017; Omari et al., 2015). Low-resolution manometry typically incorporates three to four catheter sensors with a fixed distance of typically 2 and 3 cm between sensors; one of these sensors is located within the UES (Salassa, DeVault, & McConnel, 1998). Limitation in spatial resolution is particularly relevant for assessment of UES function. The low-resolution sensor initially located within the UES may be displaced as the sphincter moves superiorly during swallowing; thus, failing to record UES pressure after this point. HRM and HRIM offer the advantage of higher spatial resolution due to the increased number of catheter sensors (Hoffman et al., 2012). The closely spaced HRM sensors allow for increased continuity in recording UES pressure (S. Meyer et al., 2012). While visualisation and pressure modalities can be applied in isolation, concurrent application of both modality types may be used in the assessment of the UES. Such combined modalities include manofluorography (Nativ-Zeltzer, Kahrilas, & Logemann, 2012; Nativ-Zeltzer et al., 2016) and mano-videoendoscopy (Karahö, Satoh, Nakajima, Nakayama, & Kohno, 2015).

Other than visualisation techniques and modalities for pressure analysis, there is preliminary research exploring the use of a functional lumen imaging probe for evaluation of UES distensibility (Regan, Walshe, Rommel, & McMahon, 2013; Regan, Walshe, Rommel, Tack, & McMahon, 2013; Rommel & Hamdy, 2016). Further, electrical activity of the cricopharyngeus has been evaluated using EMG (Ertekin & Aydogdu, 2002; Ertekin et al., 1995; Halum et al., 2006).

While some modalities, such as videofluoroscopy, are typically applied in clinical practice, other technologies such as EMG, MRI, or CT are mainly used in research settings. Different technologies provide unique information about UES function; the use of different instrumentation may be indicated depending on the clinical or research question (Ahuja & Chan, 2016; Logemann, 1998). Importantly, advantages and limitations of each technology need to be appreciated when considered for application. Further, as for any instrumentation

used in medical fields, validity and reliability are key aspects to consider (George, Batterham, & Sullivan, 2000; Kimberlin & Winterstein, 2008; Portney & Watkins, 2009). Validity provides information about whether a device measures what it is intended to measure. Reliability is an indication of the degree to which measurements can be derived with consistency over time and condition. While technology may be reliable without being valid, valid instrumentation requires a high degree of reliability (George et al., 2000; Portney & Watkins, 2009). For interpretation of published reliability data, the classification by Portney and Watkins (2009) will be used: poor reliability ( $ICC < 0.50$ ), moderate reliability ( $ICC 0.50 - 0.75$ ), and good reliability ( $ICC > 0.75$ ). The following sections review the use of videofluoroscopy, ultrasound, HRM, and HRIM in the assessment of UES function.

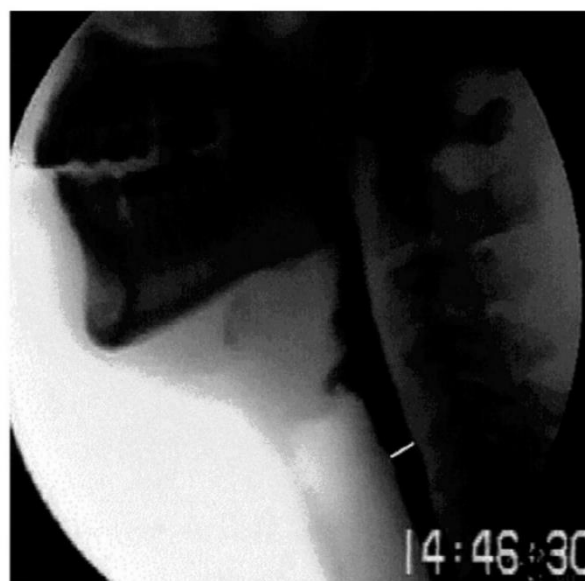
## **5.1. Videofluoroscopy**

Videofluoroscopy has been used for swallowing assessment since the 1980s (Logemann, 1998). Some have termed it gold-standard instrumentation for swallowing evaluation (Rugiu, 2007). A videofluoroscopic swallowing study is a “dynamic continuous radiological examination of the anatomy and function of the oral cavity, pharynx and UES opening” (Rommel & Hamdy, 2016, p. 49). Using videofluoroscopy, two-dimensional imaging of the oral, pharyngeal, and oesophageal stages of swallowing can be performed in lateral and anterior-posterior plane (Logemann, 1998; Steele, 2015). Videofluoroscopy provides temporal and spatial information about swallowing biomechanics. Further, observation of bolus flow during swallowing is possible by use of a radio-opaque bolus, such as barium (Logemann, 1998; Rugiu, 2007; Steele, 2015). Visualisation of the bolus allows for evaluation of bolus transit times and of the timing of individual biomechanical features in relation to bolus position. Additionally, bolus penetration and aspiration into the airway or bolus residue can be visualised (Logemann, 1998; Rugiu, 2007). The fluoroscopic images may be analysed frame-by-frame or in real-time after completion of the study (Logemann, 1998; Rugiu, 2007). Analysis of videofluoroscopic images may be qualitative or quantitative; the use of qualitative interpretation methods is more common in clinical practice, however qualitative methods are limited by subjectivity (Daniels & Huckabee, 2014; Rommel & Hamdy, 2016).

### **5.1.1. Assessment of UES Function**

Qualitative and quantitative videofluoroscopic evaluation of UES function during swallowing may inform about extent, duration, and timing of UES opening (Kendall & Leonard, 2002; Y. Kim, Park, Oommen, & McCullough, 2015) and of hyolaryngeal displacement (Sia, Carvajal,

Carnaby-Mann, & Crary, 2012; Steele et al., 2011). Protocols used for qualitative interpretation may include binary or multilevel ratings of swallowing events such as UES opening and hyolaryngeal excursion. A binary rating for UES opening extent may include the categories “incomplete” or “complete” while a multilevel ratings for the timing of UES opening may comprise the categories “early”, “normal”, or “late” (Stoeckli, Huisman, Seifert, & Martin-Harris, 2003, p. 54). A protocol that aims for more objectivity by assigning numbers to qualitative ratings is the MBS-Imp measurement tool for swallow impairment (Martin-Harris et al., 2008). In contrast, objective measures are used for quantification of temporal and spatial aspects of UES opening (Kendall & Leonard, 2002; Y. Kim et al., 2015; Leonard et al., 2000), and of hyolaryngeal excursion (Leonard et al., 2000; Sia et al., 2012; Steele et al., 2011). A reported example of a timing measure of UES opening is “the time at which the pharyngo-esophageal sphincter has reached its widest opening” (Kendall et al., 2000, p. 75) while a spatial measure of UES opening is “maximal distention for bolus passage” (Leonard et al., 2000, p. 147) (Figure 7).



**Figure 7.** Videofluoroscopic lateral image of the head and neck. The white line represents upper oesophageal sphincter (UES) opening diameter at maximal distention (Leonard et al., 2000)<sup>9</sup>.

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<sup>9</sup> From “Structural displacements in normal swallowing: A videofluoroscopic study” by Leonard et al. (2000), *Dysphagia*, 15 (3), p. 149. Reprinted with permission from Springer Nature.

For quantitative measurements, image calibration is required to account for image magnification and distortion (Sia et al., 2012; Steele, 2015). Further, for measurement of hyoid excursion, the use of reference axes has been reported to account for head movements during swallowing (Y. Kim & McCullough, 2008; Logemann et al., 2000; Paik et al., 2008). Thus, when comparing data across studies, it is important to appreciate these important methodological distinctions (Sia et al., 2012).

The reliability of videofluoroscopy for evaluation of UES function may be limited, especially with regard to intra- and inter-rater reliability of perceptual, subjective ratings of UES opening and/or hyolaryngeal excursion (Bryant, Finnegan, & Berbaum, 2012; D. H. Kim et al., 2012; McCullough et al., 2001; Scott, Perry, & Bench, 1998; Stoeckli et al., 2003). For example, there is evidence for insufficient inter-rater reliability of measurements of UES and hyolaryngeal excursion ( $\kappa = 0.03 - 0.42$ ), even when raters could discuss the videofluoroscopic recordings with team members not involved in the study (Stoeckli et al., 2003). Of note, in this study, raters were not informed about the clinical history of the patients. However, in clinical practice, videofluoroscopic examination commonly follows clinical swallowing assessment and information is paired for interpretation. Thus, reliability was potentially decreased due to isolated information, but requires confirmation in future research. Martin-Harris and colleagues reported high intra- and inter-rater reliability for trained raters for videofluoroscopic analysis using the modified barium swallowing study evaluation tool that specifically targeted increased objectivity in qualitative ratings (Martin-Harris et al., 2008). While reliability may be problematic for subjective ratings, there is evidence to suggest good reliability for objective temporal and spatial measures of UES function (Leonard, 2018; R. Leonard, K. Kendall, & S. McKenzie, 2004a; Leonard et al., 2000; Martin-Harris et al., 2008; Nordin, Miles, & Allen, 2017). Good inter-rater reliability was reported for maximum hyoid displacement ( $r > 0.90$ ), hyolaryngeal approximation ( $r = 0.75$ ), maximal extent of UES opening ( $r > 0.90$ ), and UES opening duration ( $r > 0.90$ ) in healthy subjects (Leonard, 2018; Leonard et al., 2004a; Leonard et al., 2000). Further, good reliability of hyoid excursion and laryngeal displacement was documented for patients with dysphagia (intra-rater ICC  $> 0.92$ , inter-rater ICC = 0.77) (Sia et al., 2012). A study by Nordin and colleagues (2017) showed an association between increased reliability and increased experience with derivation of objective measures. This highlights the importance of rater training for optimised reliability.

### ***5.1.2. Advantages and Limitations***

Videofluoroscopic imaging provides numerous advantages in the assessment of UES function. It allows for evaluation of UES opening in the context of pharyngeal biomechanics, including hyolaryngeal excursion; this is of value as pharyngeal swallowing is a coordinated sequence of events (Rugiu, 2007). Information about bolus flow through the UES can be gained and rehabilitation or compensation strategies for UES dysfunction, such as effortful swallowing or head rotation can be trialled and evaluated during imaging (Rugiu, 2007). Despite the undisputed value of videofluoroscopic swallowing studies, there are limitations to consider. Videofluoroscopic imaging does not provide information about underlying aetiologies for UES dysfunction, such as failed intra-swallow UES relaxation versus impaired hyolaryngeal excursion; thus, its use for differential diagnostics of UES impairment is limited. Further, quantification of pharyngeal residue as a potential consequence of UES dysfunction is limited by the two-dimensional nature of videofluoroscopy (Pearson, Molfenter, Smith, & Steele, 2013). Videofluoroscopy exposes patients to radiation (Daniels & Easterling, 2017; Rommel & Hamdy, 2016); hence, its use for prolonged studies, repeated testing or for frequent application in vulnerable patient populations, such as children, is limited (Rugiu, 2007). Further, subjects with movement impairment or poor cooperation may not be eligible for this procedure (Daniels & Easterling, 2017; Rugiu, 2007). As videofluoroscopy is an instrument with limited mobility (Rugiu, 2007), bedside videofluoroscopic evaluation for patients who are critically ill is not possible. Further, access to a videofluoroscopy suite is potentially challenging for patients living in non-urban areas as this technology may be difficult to access (Rugiu, 2007).

### **5.2. Ultrasound**

Brightness-mode ultrasound provides two-dimensional real-time video-imaging of structures and muscles involved in swallowing (Watkin, 1999). Grey-scale imaging or B-mode is the most commonly used mode for ultrasound examination (Kossoff, 2000). The frequencies of sound waves used in medical fields range typically from 2 to 15 MHz (Jensen, 2007). Transducers produce an ultrasound beam by converting electrical energy into ultrasonic energy (Aldrich, 2007). Transducers differ in the frequencies they generate. The linear transducer produces rectangular images while the curvilinear transducer obtains a sector image (Jensen, 2007; Kundra, Mishra, & Ramesh, 2011). The ultrasound energy travels as sound waves through body tissue (Aldrich, 2007; Kossoff, 2000) with a reflection of sound waves occurring at the interface of biologic tissue with different acoustic impedance. This reflection, also called

an echo, is then collected by the transducer on return (Aldrich, 2007). Great differences in impedance are found between soft tissue and bony structures or between soft tissue and air-filled space (Kristensen, 2011). Such large differences in acoustic impedance result in total reflection of the ultrasound beam and show white on the image. Weak echoes occur if two tissues have similar acoustic impedance, such as tissue and water (Epstein & Stone, 2005). Weak echoes appear grey on the image (Aldrich, 2007). Depending on tissue properties, sound propagation is enhanced or decreased. If sound encounters hyperechoic tissue, such as fat or bone, substantial sound waves are reflected as an echo (Kundra et al., 2011; M. Singh et al., 2010). Conversely, hypoechoic tissues, including fluids or moisture enhance sound propagation (Kristensen, 2011; Kundra et al., 2011; M. Singh et al., 2010; Stone, 2005).

The use of ultrasound for swallowing assessment has been reported since the 1970s (Chi-Fishman, 2005; Stevens, 1978) and has included investigations of structure, morphology or movement of the submental muscles (Emshoff, Bertram, & Strobl, 1999; Shimizu et al., 2016), tongue (Hsiao, Chang, Chen, Chang, & Wang, 2012; Li et al., 2015), pharynx (J.-H. Kim & Kim, 2012; J. L. Miller & Watkin, 1997), hyoid (Hsiao et al., 2012; Y. S. Lee, Lee, Kang, Yi, & Kim, 2016), larynx (Ahn et al., 2015; Kuhl, Eicke, Dieterich, & Urban, 2003), UES (Moriniere et al., 2013), valleculae and pyriform sinuses (K. Singh et al., 2017). Further, studies report the use of ultrasound for detection of pharyngeal residue (Miura et al., 2016; Miura et al., 2018) and aspiration (Miura et al., 2014; Miura et al., 2018). Ultrasound measures associated with swallowing have been derived in healthy participants (Kuhl et al., 2003; J. L. Miller & Watkin, 1997) and in patients with stroke (Huang, Hsieh, Chang, Chen, & Wang, 2009; J.-H. Kim & Kim, 2012), Parkinson's disease (E. H. Oh, Seo, & Kang, 2016), and ALS (Nakamori et al., 2016; Noto et al., 2017).

### ***5.2.1. Assessment of UES Function***

The use of ultrasound in the evaluation of UES opening is not common. One study reported normative data for morphological and functional UES measurements during water swallowing in 25 healthy adults (Moriniere et al., 2013). This study documented that “the UES was recognized by its specific C-shaped anatomical structure attached to the cricoid cartilage” (p. 322). Reported morphological parameters of the UES included outer cross-sectional diameter of the closed and open UES, inner cross-sectional diameter of the open UES, thickness of the UES musculature during opening, and anterior and lateral displacement of the UES. Functional measurements involved UES opening duration, UES displacement duration, time from onset

of UES displacement to opening, and time from UES closure to return to resting position. Notably, measurements were not validated, and the study lacked report of measurement reliability. Hence, more research is needed to explore the viability of ultrasound in the assessment of UES.

While there is little data on direct ultrasound assessment of the UES; there is more research documenting ultrasound assessment of hyolaryngeal displacement in healthy subjects and patient populations. Reported ultrasound measures of hyolaryngeal displacement include hyoid excursion (Y.-C. Chen, Hsiao, Wang, Fu, & Wang, 2017; Chi-Fishman & Sonies, 2002a, 2002b; Dejaeger & Pelemans, 1996; Hsiao et al., 2012; Y. S. Lee et al., 2016; Macrae, Doeltgen, Jones, & Huckabee, 2012; Perry, Winkelman, & Huckabee, 2016; Rocha, da Silva, & Berti, 2015; Scarborough et al., 2010; Shawker, Sonies, Hall, & Baum, 1984; Sonies, Wang, & Sapper, 1996; Yabunaka et al., 2011) and thyrohyoid approximation (Ahn et al., 2015; Huang et al., 2009; Kuhl et al., 2003).

Validity data of ultrasound in the assessment of swallowing are emerging. There are data to suggest that ultrasound is valid in the assessment of hyolaryngeal excursion, as compared to videofluoroscopy. A strong correlation between ultrasound and videofluoroscopic measures of hyoid excursion during water swallows was reported in 12 dysphagic stroke patients (ICC = 0.804) (Hsiao et al., 2012) and in 10 dysphagic patients with diverse underlying aetiologies (ICC rater 1 = 0.815, ICC rater 2 = 0.916) (Y.-C. Chen et al., 2017). Both studies (Y.-C. Chen et al., 2017; Hsiao et al., 2012) are based on small sample sizes and raise some questions regarding data analysis and data interpretation as information regarding statistical analysis lacked. Thus, further data are needed to validate ultrasound measures of hyoid excursion and thyrohyoid approximation against videofluoroscopy based on larger sample sizes of dysphagic patients and in healthy populations. Other than validation against videofluoroscopy, sensitivity and specificity of ultrasound measures of hyolaryngeal excursion in detecting dysphagia have been reported. It has been proposed that hyoid displacement below 1.5 cm, as assessed using ultrasound, may serve as a cut-off value for detecting tube-feeding dependent dysphagia in stroke patients, with a sensitivity and specificity of 0.73 and 0.66, respectively (Hsiao et al., 2012). Notably, tube-feeding dependency was defined clinically using the functional oral intake scale rather than based on physiological criteria. This may be considered a methodological limitation of the study. Further, a cut-off value of 13.5 mm for hyoid excursion in patients with dysphagia was reported to predict presence or absence of penetration and aspiration, according to the penetration-aspiration scale (Rosenbek, Robbins, Roecker, Coyle,



& Wood, 1996), with a sensitivity of 0.84 and a specificity of 0.81 (Y. S. Lee et al., 2016). Huang and colleagues (2009) reported a cut-off value of < 40% for thyrohyoid approximation to detect dysphagia in stroke patients with a sensitivity of 0.75 and a specificity of 0.77. Of note, dysphagia was defined based on clinical evaluation. Thus, in future studies, the use of objective measures of dysphagia would be of value. These studies provide early data to evaluate validity of ultrasound, yet further data are needed. While validity of instrumentation is critical, quantification of reliability is also required.

Published reliability data are depicted in Table 1. Good intra-rater reliability and moderate to good inter-rater reliability, based on interpretation criteria published by Portney and Watkins (2009), has been reported for ultrasound assessment of hyoid excursion in healthy individuals (Hsiao et al., 2012; Macrae et al., 2012), and in patients with dysphagia (Y.-C. Chen et al., 2017). Further, good intra- and inter-rater reliability of thyrohyoid approximation was reported in healthy participants (Huang et al., 2009). While all of these studies report promising reliability, only the study by Macrae and colleagues (2012) provides confidence intervals (CI) that inform about the precision of the reliability estimates. While some studies reported on reliability of the entire process of data collection including the scanning procedure, image selection, and measurement (Hsiao et al., 2012; Huang et al., 2009), other studies documented measurement reliability in isolation that excludes the scanning procedure (Macrae et al., 2012) or the scanning procedure and image selection from reliability analysis (Y.-C. Chen et al., 2017). Although measurement reliability provides important information about reliability of a measurement technique, in a clinical setting, ultrasound measures will be acquired by different clinicians. Hence, reliability data regarding the entire process of data acquisition may be more clinically relevant. Most studies assessed reliability for a single consistency, either for saliva (Macrae et al., 2012) or for water swallows (Y.-C. Chen et al., 2017; Hsiao et al., 2012; Huang et al., 2009). Since it is unknown whether bolus consistency impacts reliability, study results cannot be generalised to other consistencies. Future research is needed to assess the effect of bolus consistency on reliability. Notably, the majority of studies reporting on reliability of hyoid excursion and thyrohyoid approximation fail to provide information about intensity or duration of the rater training (Hsiao et al., 2012). If ultrasound is to translate into clinical practice in the future, this information would be of use for establishment of training programmes for clinicians. While published reliability data seem promising, it should be considered that studies are based on a small sample size of participants and raters, as depicted in Table 1. Thus, more research is needed to explore reliability of ultrasound in the assessment of swallowing.

**Table 1.** Reported reliability for hyoid excursion and thyrohyoid approximation in the literature

<b>Authors</b>	<b>Measure</b>	<b>Components of data extraction considered for analysis</b>	<b>Participants</b>	<b>Number of raters involved in inter-rater reliability</b>	<b>Intra-rater ICC</b>	<b>Inter-rater ICC</b>
Hsiao et al. (2012)	Hyoid excursion (Absolute displacement)	Data acquisition	10 healthy subjects	2	0.927 0.842	0.806
Macrae et al. (2012)	Hyoid excursion (Absolute and percentage displacement)	Image selection and measurement	5 healthy subjects	3	0.90 0.93	0.64 0.70
Y.-C. Chen et al. (2017)	Hyoid excursion (Absolute displacement)	Image measurement	10 dysphagic patients	2	0.996 0.959	0.892
Huang et al. (2009)	Thyrohyoid approximation (Percentage displacement)	Data acquisition	5 healthy subjects	2	0.974 0.989	0.983

*Note.* ICC = intraclass correlation coefficient

### 5.2.2. Methodological Considerations

The imaging principles of ultrasound, as discussed in section 5.2, have implications for the use of ultrasound in the assessment of swallowing including hyolaryngeal excursion. Ultrasound waves are strongly reflected at hyperechoic tissue. Thus, the hyoid bone, that contains a minimal amount of water, cannot be directly visualised. Yet, a hypoechoic acoustic shadow cast behind the hyoid can be identified on the image and used as a landmark for measurement for hyoid excursion (Kossoff, 2000; M. Singh et al., 2010; Walker, Cartwright, Wiesler, & Caress, 2004) (Figure 8). For bolus swallowing, reflection principles suggest that characteristics of the bolus may impact its visibility in the oral cavity. For example, water in the oral cavity may not be clearly shown on the image as the interface between tongue and water does not produce strong echoes (Epstein & Stone, 2005). Thus, careful selection of bolus types is warranted for measures where visualisation of the bolus is of importance. Other than imaging principles, methodological aspects of data acquisition are important to consider in the assessment of hyolaryngeal displacement.



**Figure 8.** Ultrasound image depicting the black shadow cast by the mandible (at the left of the image) and the shadow cast by the hyoid (at the right of the image).

Derivation of quantitative ultrasound measurements of swallowing measures, including hyolaryngeal excursion, is a procedure that includes several steps. The procedure of data acquisition can be divided into the scanning process, image selection for measurement, and derivation of measurements. Methodology of each of these aspects is of importance as methods may impact findings. For example, pressure application of the transducer on the skin and underlying tissue during scanning may affect data. If soft tissue is depressed due to increased

pressure, the validity of measurements may be reduced (Stone, 2005). Further, methodology of transducer placement is a critical aspect to consider. Minimal but constant contact between transducer and skin is critical for optimal imaging. Uncontrolled movements of the subject during scanning or inconsistent transducer placement may affect measurements. Thus, the use of transducer or head stabilisation techniques has been reported in the literature. The effect of such methods has been mainly evaluated for tongue assessment (C.-L. Peng, Jost-Brinkmann, & Miethke, 1996; Stone, 2005; Stone & Davis, 1995). For hyoid excursion, Perry and colleagues (2016) reported no convincing evidence that fixed transducer placement results in increased measurement accuracy as compared to hand-held transducer placement.

Regarding measurement techniques, differences across studies can be appreciated. Hyoid excursion was quantified based on absolute measurements (Y.-C. Chen et al., 2017; Hsiao et al., 2012; Macrae et al., 2012) and as the percentage change from the distance at rest to maximal displacement (Macrae et al., 2012). Thyrohyoid approximation is commonly reported as a relative measurement (Ahn et al., 2015; Huang et al., 2009; Kuhl et al., 2003). Of the studies reporting reliability data for hyoid excursion, detailed information about measurement techniques are documented in some studies (Y.-C. Chen et al., 2017; Macrae et al., 2012). The study by Hsiao and colleagues (2012) provided insufficient information regarding measurement techniques to be replicated. Similarly, the one study reporting measurement reliability of thyrohyoid approximation lacked detailed description of measurement techniques (Huang et al., 2009). Reporting methodology should be standard in future studies. More research is needed to evaluate different measurement techniques for swallowing measures and to compare reliability across different measurement techniques.

### ***5.2.3. Advantages and Limitations***

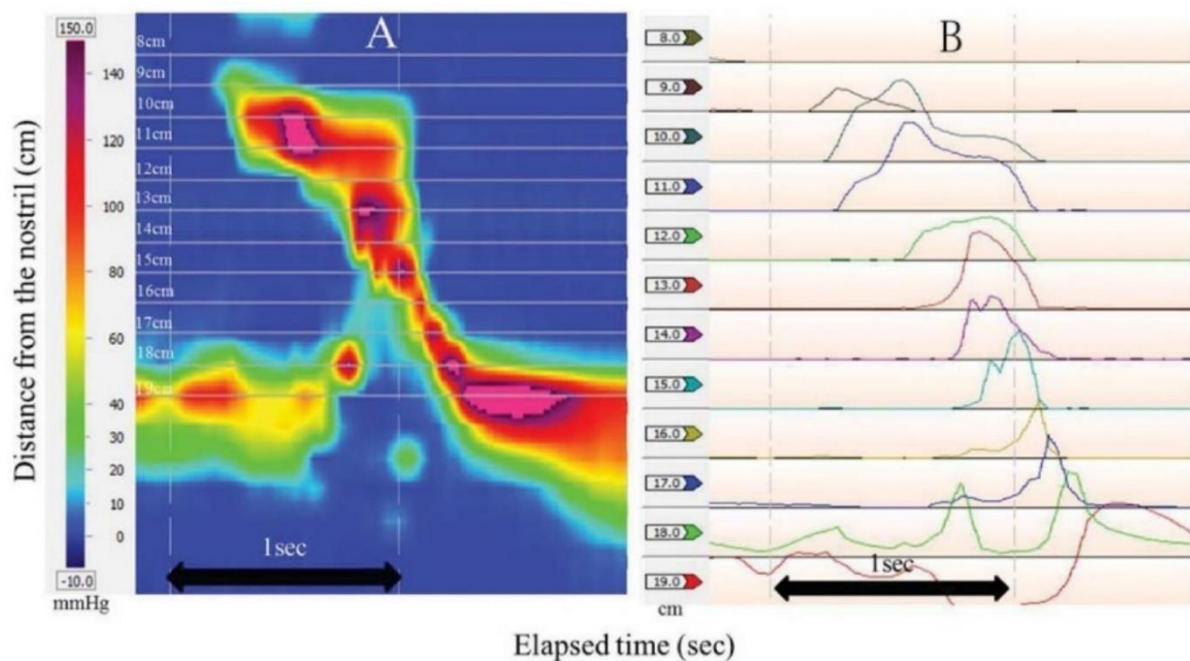
The use of ultrasound in the comprehensive assessment of UES function provides benefits as a non-invasive, radiation-free procedure. Thus, it can be beneficial for repeated use for diagnostics (Logemann, 1998; Watkin, 1999) or used as a biofeedback modality, particularly for vulnerable patient groups, including children (Watkin, 1999). Compared to videofluoroscopy, standard diagnostic ultrasound is portable (Watkin, 1999) and may provide a viable instrumental assessment for evaluation of hyolaryngeal excursion for patients who are unable to mobilise out of bed or for patients who cannot access a videofluoroscopy suite. The use of ultrasound is possible in patients with restricted alertness as less cooperation is needed

for this procedure as compared to videofluoroscopy; further, this is a low-cost procedure in comparison to other instrumentation.

However, despite numerous advantages, there are limitations to be acknowledged in the use of ultrasound for assessment of UES function. As stated previously, the one study evaluating UES directly was limited by an absence of validity and reliability measurements. The potential for direct visualisation of the UES needs to be further clarified. Thus, application of ultrasound for UES assessment is currently limited to indirect UES assessment, including measurements of hyolaryngeal excursion. Compared to videofluoroscopy, ultrasound does not inform about coordination of UES opening and hyolaryngeal displacement or about bolus flow through the UES. Further, one specific region of the head and neck can only be imaged at a time, thus, separate evaluation of hyoid excursion and thyrohyoid approximation is common. However, hyoid excursion and thyrohyoid approximation are interdependent biomechanical events, thus, overall assessment of hyolaryngeal displacement may be considered a limitation of ultrasound. A further challenge is decreased image clarity at the periphery of the image section, which may impact measurements (Steele, 2015). The lack of translation of ultrasound for swallowing assessment, including hyolaryngeal excursion, to clinical practice suggests that size and cost of standard diagnostic equipment limit its use. Newer devices that are smaller and less expensive may increase the potential for clinical translation. As stated previously, validity data are still emerging and more research is needed to evaluate whether ultrasound is valid as compared to videofluoroscopy.

### **5.3. Pharyngeal High-resolution Manometry (HRM)**

Pharyngeal HRM provides quantitative pressure data in the assessment of swallowing (Jungheim, Miller, & Ptak, 2013; Knigge et al., 2014). HRM catheters house between 20 and 36 sensors, with a maximum distance of 1 cm between sensors. Each sensor is typically composed of 12 - 16 individual segments that produce a circumferential average pressure. Average values are displayed either as line traces or as spatiotemporal contour plots. Both visualisation modes depict three dimensions: the temporal dimension on the X-axis, the spatial dimension on the Y-axis, and the pressure dimension as line traces or contour plots (Nativ-Zeltzer et al., 2012) (Figure 9). The contour plots allow for continuous visualisation of pressure in the aerodigestive tract, with interpolation between neighbouring sensors (Kahrilas & Sifrim, 2008; Nativ-Zeltzer et al., 2012).



**Figure 9.** Illustration of a swallow on high-resolution manometry (HRM). The swallow is depicted in the contour mode on the left (A), and as wave tracings on the right (B) (Matsubara, Kumai, Samejima, & Yumoto, 2014)<sup>10</sup>.

### 5.3.1. Assessment of UES Function

HRM was originally developed for assessment of oesophageal motility. Since 2006, this technique has been increasingly used for evaluation of pharyngeal swallowing (Ghosh, Pandolfino, Zhang, Jarosz, & Kahrilas, 2006; Knigge et al., 2014; Takasaki et al., 2008). Information of UES function during swallowing, as assessed using pharyngeal HRM, includes magnitude, timing, and duration of UES relaxation (Knigge et al., 2014; J. P. Meyer et al., 2016; Rice & Shay, 2011; Takasaki et al., 2008). Further, data about pressure at rest can be gained (Lan, Xu, Dou, Wan, Yu, et al., 2013; C.-H. Park et al., 2017) and the axial length of the UES may be quantified (Menezes, Herbella, & Patti, 2015; Silva et al., 2013).

Assessment of UES function using pharyngeal HRM has been documented in healthy subjects and patients populations, including stroke (Juan et al., 2013; Lan et al., 2015; Lan, Xu, Dou, Wan, & Yu, 2013), head and neck cancer (Yamaguchi et al., 2017), myotonic dystrophy (Jungheim, Kuhn, & Ptok, 2015), or degenerative diseases including Parkinson's disease

<sup>10</sup> From "Swallowing pressure and pressure profiles in young healthy adults" by Matsubara et al. (2014), The Laryngoscope, 124 (3), p. 712. Reprinted with permission from John Wiley and Sons.

(Derrey et al., 2015; Jones, Michelle, & Timothy, 2016) and ALS (Noh, Park, Park, Moon, & Jung, 2010; Takasaki, Umeki, Enatsu, Kumagami, & Takahashi, 2010). HRM studies have evaluated UES pressure response to compensatory strategies such as chin tuck (Matsubara, Kumai, Kamenosono, Samejima, & Yumoto, 2016; McCulloch et al., 2010) and head turn (Takasaki, Umeki, Kumagami, et al., 2010), as well as swallowing manoeuvres including effortful swallowing (Hoffman et al., 2012; Takasaki et al., 2011) and Mendelsohn manoeuvre (Hoffman et al., 2012). The effect of neuromuscular stimulation on UES pressure was explored in a study using HRM by Jungheim, Janhsen, and colleagues (2015).

Using pharyngeal HRM, normative data for UES parameters have been established (Ghosh et al., 2006; Jungheim, Schubert, et al., 2015; Nativ-Zeltzer et al., 2016; Silva et al., 2013; Takasaki et al., 2008). Of the studies reporting normative data, one reported data for different age groups (Nativ-Zeltzer et al., 2016) while another documented data separately for males and females (Takasaki et al., 2008). Such data are of value considering research suggesting an effect of age (Nativ-Zeltzer et al., 2016; Yoon et al., 2014) and sex (Nativ-Zeltzer et al., 2016) on intra-swallow UES parameters. As depicted in Table 2, reported UES parameters differ significantly across studies. This may reflect a current lack of consensus on which measures best describe UES function. Thus, more research is required to evaluate key variables for identification of UES pathophysiology in this relatively new and rapidly evolving instrumentation.

**Table 2.** Selection of results from published normative data for UES parameters

Authors	Subjects	Bolus	Statistics	Amplitude Measures	Temporal Measures	Other Measures
Ghosh et al. (2006)	75	Liquid: 1 mL (dry); 5mL; 10 mL; 20 mL	Mean $\pm$ SD	<i>Minimum relaxation pressure (mmHg):</i> $3.18 \pm 6.33$ (1 mL); $5.42 \pm 4.53$ (5 mL); $8.84 \pm 4.84$ (10 mL); $10.32 \pm 5.31$ (20 mL)  <i>Median intrabolus pressure during relaxation interval (mmHg):</i> $5.93 \pm 6.57$ (1 mL); $7.58 \pm 4.40$ (5 mL); $11.30 \pm 4.67$ (10 mL); $13.80 \pm 4.76$ (20 mL)	<i>Relaxation interval (s):</i> $0.32 \pm 0.09$ (1 mL); $0.41 \pm 0.09$ (5 mL); $0.45 \pm 0.13$ (10 mL); $0.50 \pm 0.11$ (20 mL)	<i>Deglutitive sphincter resistance (mmHg/s):</i> $22.60 \pm 28.70$ (1 mL); $20.46 \pm 15.33$ (5 mL); $31.40 \pm 32.50$ (10 mL); $33.25 \pm 19.49$ (20 mL)
Takasaki et al. (2008)	33	Dry  Liquid: 5 mL	Mean $\pm$ SD	<i>Maximum resting pressure (mmHg):</i> Dry: $172.7 \pm 73.8$ (males); $149.2 \pm 68.7$ (females)  Liquid: $236.1 \pm 78.9$ (males); $243.7 \pm 87.4$ (females)		<i>Length from nasal nostril to maximum UES pressure (cm):</i> $19.1 \pm 1.3$ (males); $17.0 \pm 1.2$ (females)  <i>Length of UES resting pressure zone:</i> $4.0 \pm 0.7$ (males) $3.6 \pm 0.6$ (females)
Silva et al. (2013)	40	Liquid: 5 mL	Median (IQR)	<i>Basal pressure (mmHg):</i> 76.3 (58.2 – 109.1)  <i>Residual pressure (mmHg):</i> 4.4 (1.2 – 6.9)	<i>Relaxation time to nadir (ms):</i> 201.0 (144.0 – 241.0)  <i>Relaxation duration (ms):</i> 678.0 (636.0 – 757.0)  <i>Recovery time (ms):</i> 501.0 (394.0 – 549.0)	<i>Extension (cm):</i> 3.0 (2.6 – 3.6)



Jungheim, Schubert, et al. (2015)	29	Liquid: 2 mL	Mean ± SD	<i>Maximum UES pressure before relaxation (mmHg):</i> 82.7 ± 53.6  <i>Maximum pressure after relaxation (mmHg):</i> 205.8 ± 64.0  <i>Residual pressure (mmHg):</i> -24.6 ± 9.4  <i>Resting pressure (mmHg):</i> 42.5 ± 18.7	<i>Relaxation time (ms):</i> 681.6 ± 86.8  <i>Activity time (ms):</i> 822.8 ± 165.4
Nativ-Zeltzer et al. (2016)	44	Liquid: 1mL; 5 mL; 10 mL  Pudding: 3 mL  Cookie	Mean ± SD	<i>UES integrated relaxation pressure (mmHg):</i> Liquid: 1 ± 8 (1 mL); 0 ± 6 (5 mL); 0 ± 7 (10 mL)  Pudding; Cookie: 3 ± 8; 6 ± 8  <i>Maximum post-deglutitive UES contraction (mmHg):</i> Liquid: 201 ± 59 (1 mL); 209 ± 60 (5 mL); 212 ± 56 (10 mL)  Pudding; Cookie: 219 ± 83; 218 ± 51	<i>Post-deglutitive UES contractile integral (mmHg/s/cm):</i> Liquid: 407 ± 185 (1 mL); 407 ± 170 (5 mL); 390 ± 181 (10 mL)  Pudding: 485 ± 206  Cookie: 557 ± 293

Note. UES = upper oesophageal sphincter, SD = standard deviation, IQR = interquartile range

### **5.3.2. Methodological Considerations**

Methodological differences are apparent in studies using pharyngeal HRM, including those reporting normative data. The methodological variability of data acquisition and data analysis likely reflects limited standards in methodology, as the use of pharyngeal HRM is in early stages. Importantly, there is emerging evidence that methodology of data acquisition and data analysis may impact data interpretation. For example, regarding the width of the catheter in situ, it has been reported that pressure at the UES may be affected by increasing catheter diameter (Jungheim, Miller, & Ptak, 2013; Jungheim, Schubert, et al., 2015; Nativ-Zeltzer et al., 2016). Nativ-Zeltzer and colleagues (2016) acquired UES parameters including UES integrated relaxation pressure, post-deglutitive UES contractile integral, and maximum UES pressure using a 2.75 mm catheter. The authors postulated that these variables were significantly lower compared to published data collected using a 4.2 mm catheter. Further, evidence suggests that use of topical anaesthesia for HRM catheter placement may impact pharyngeal pressure (Guiu Hernandez, Gozdzikowska, Apperley, & Huckabee, 2017). Future research is needed to evaluate the impact of topical anaesthesia on UES pressure and to clarify differences in regard to dosage and application location. Another methodological aspect of data acquisition concerns an adjustment period to the catheter in situ following catheter placement. While time for adjustment has been recommended for low-resolution manometry (Castell & Castell, 1993), there are no recommendations for pharyngeal HRM. A longer duration for adjustment may be required for larger catheters; yet, future research is needed to clarify this. Further, the body position of the participants during study performance may affect data. While there are several studies evaluating the effect of body position on oesophageal parameters (Hiranyatheeb et al., 2017; Sweis et al., 2011; Xiao, 2012), there is one study suggesting that UES measurements in healthy subjects may be affected by the participant's body position. Rosen, Abdelhalim, Jones, and McCulloch (2018) derived UES measurements in 10 healthy subjects in six body positions. Significantly higher minimum pressure was found at 45° and 90° compared to a fully inverted position.

As for the bolus used for swallowing evaluation, an effect of consistency has been reported in healthy subjects. Nativ-Zeltzer and colleagues (2016) found increased integrated UES relaxation pressure and post-deglutitive contractile integral for heavier consistencies such as pudding and cookie as compared to liquid swallows. These findings contrast data suggesting no difference between UES relaxation duration for water, barium, and yoghurt boluses (Yoon et al., 2014). Other than bolus consistency, bolus volume has been found to affect UES

measurements. In a study by Lin and colleagues (2014), UES pressure was examined in 34 healthy subjects using pharyngeal HRM. The study revealed an effect of bolus volume for UES residual pressure and UES relaxation duration while no effect was found for maximum pre-opening and post-closure UES pressure.

Other than methodological variability in regard to data acquisition, varying methods of data analysis can also be appreciated in studies using pharyngeal HRM. Different methods in data analysis likely have an impact on data interpretation. While some studies use the analysis software intrinsic to the recording system (Lan et al., 2017; Matsubara et al., 2014; Nativ-Zeltzer et al., 2016), other studies utilise customised external MATLAB software. The use of customised analysis programme using MATLAB software for data analysis has been reported in numerous studies using HRM for assessment of pharyngeal swallowing (Hammer, Jones, Mielens, Kim, & McCulloch, 2014; Mielens et al., 2011; C.-H. Park et al., 2017). Such external analysis programmes have been developed due to limitations of the system-based software for pharyngeal swallowing. For example, for the most commonly used ManoScan™ system (Winiker, Gillman, Guiu Hernandez, Huckabee, & Gozdzikowska, 2018), the manufacturer's software ManoView™ provides automated analysis for oesophageal evaluation but only for some UES parameters. Thus, additional manual analysis is required for UES assessment (T. H. Lee, Lee, Hong, Lee, Jeon, Kim, Kim, Cho, Kim, Cho, Park, et al., 2014). Further, concerns regarding the accuracy of automated analysis of ManoView™ software have been raised (T. H. Lee, Hong, & Lee, 2014; T. H. Lee, Lee, Hong, Lee, Jeon, Kim, Kim, Cho, Kim, Cho, Park, et al., 2014). Due to the importance of methodology of data acquisition and analysis on interpretation of the data, it is critical to understand current methodological practice. The systematic review in Chapter 8 will summarise and appraise the status quo of reported methodology in studies using pharyngeal HRM.

Data on reliability are critical as a foundation for use of pharyngeal HRM in research and clinical settings. There are reliability data for UES parameters from healthy subjects and patients with dysphagia assessed using pharyngeal HRM and analysed using a customised MATLAB software for semi-automated analysis (Jones, Hoffman, et al., 2014). This study involved 23 raters with varying experience level in HRM data extraction ("expert users", "novice users", "speech-language pathologists") (p. 2). The three expert users provided a training session of 20 minutes to the 20 raters with less or no experience in HRM data extraction. According to the interpretation criteria published by Portney and Watkins (2009), this study revealed good intra- and inter-rater reliability among all raters for the UES

parameters, including two- and three-dimensional integrals of pre-opening and post-closure pressure peaks and UES relaxation pressure (intra-rater ICC: 0.87 – 1.00, inter-rater ICC: 0.85 – 0.99). While this study provides promising reliability data for one specific MATLAB analysis programme, its use is not open-access. Thus, reliability data of analysis methods available for clinical users is required. In a study by Lamvik (2016), five speech and language therapists analysed swallows of healthy subjects and dysphagic patients for assessment of reliability. The raters had varying levels of experience in HRM data extraction and attended a 20-minute training session prior to start of data analysis. Data were extracted following the clinical guide published by Knigge and colleagues (2014) based on ManoView™, the software intrinsic to the ManoScan™ recording system. UES parameters included UES resting pressure, UES nadir pressure, UES post-nadir maximum pressure, and UES nadir duration. While intra-rater reliability for UES variables was good, inter-rater reliability ranged from poor to moderate. With an ICC of 0.73, UES post-nadir maximum pressure was the most reliable UES measure across raters. UES nadir duration was the least reliable UES measure with an inter-rater ICC of 0.11. Contrasting findings are evident across the two studies evaluating reliability of an external customised and a system-based analysis method. Thus, more data are needed to explore reliability of pharyngeal HRM as good reliability is paramount for clinical use. Further, future studies are required to examine the impact of aspects such as bolus consistency on reliability.

### ***5.3.3. Advantages and Limitations***

The use of pharyngeal HRM provides advantages in the assessment of UES function, such as the objective numeric nature of data that limits subjective interpretation of findings. Data obtained using pharyngeal HRM may reveal underlying pathologic pressure patterns for UES dysfunction such as impaired UES pressure relaxation (Knigge et al., 2014); this information is important for differential diagnosis. However, HRM cannot provide information about swallowing biomechanics, including hyolaryngeal displacement. Further, potential consequences of UES dysfunction such as residue, penetration or aspiration, cannot be observed (Nativ-Zeltzer et al., 2012). As a radiation-free procedure, HRM can be repeatedly used as a diagnostic or visual biofeedback tool. A study by Jones and colleagues (Jones et al., 2019) explored the perceptions of speech-language pathologists regarding the clinical use of pharyngeal HRM. The use of HRM for biofeedback was perceived as having great potential by clinicians and was a motive for implementation of this technology in clinical practice. Due to the mobility of HRM, this technology may be utilised in patients who cannot be mobilised out

of bed. However, catheter placement requires cooperation from the patient; thus, its use for some patient populations may be limited (Knigge et al., 2014). Further, the invasive nature of the procedure limits its application in patients with risk factors related to catheter placement, such as recent facial trauma (Knigge et al., 2014). However, for those patients who are eligible for the procedure, low occurrence of side effects, such as nausea, and generally high tolerability of the procedure has been reported (Knigge, Marvin, & Thibeault, 2018).

Considering technical aspects, HRM provides benefits of higher spatial resolution, as compared to low-resolution manometry and the advantage of a higher temporal resolution, as compared to videofluoroscopy. However, a technical disadvantage of HRM is the vulnerability of solid-state catheters (Bredenoord & Smout, 2008; S. Meyer et al., 2012); sensors may malfunction and negatively impact data quality. A further technical limitation concerns the ManoScan™ system. For this system, an intrinsic measurement error has been reported. If this error is not manually corrected, the validity of data may be decreased (Lamvik, Guiu Hernandez, Jones, & Huckabee, 2016). Lastly, for the majority of catheters utilised in pharyngeal HRM studies, pressure values represent an average pressure from circumferential sensors; these data may have limited informative value, considering potential pressure asymmetry in the UES (J. P. Meyer et al., 2016).

Other limitations of HRM concern analysis of data. As stated previously, an upward movement of the UES (Kahrilas et al., 1988) and of the catheter (Kahrilas et al., 1988; Yoon et al., 2014) has been observed during swallowing. Notably, it has been reported that the UES and catheter move asynchronously with a greater displacement of the UES compared to the catheter (Jones, Ciucci, Hammer, & McCulloch, 2016; Nativ-Zeltzer et al., 2016). Thus, it is challenging to determine which sensors to consider for analysis. Further, not only limited automated system-based analysis options but also potential errors in automated analysis of UES parameters (T. H. Lee, Hong, et al., 2014) highlight the need for further development of analysis methods to increase applicability of pharyngeal HRM in the assessment of UES function.

#### **5.4. Pharyngeal High-resolution Impedance Manometry (HRIM)**

Pharyngeal HRIM provides a “visual depiction of pressure flow during pharyngeal deglutition” (Cock & Omari, 2017, p. 2). Bolus transit is mapped based on alterations in electrical conductivity related to bolus passage (Kuo, Holloway, & Nguyen, 2012). Electrical impedance is measured between closely located electrodes on the catheter. Depending on the content that surrounds the electrodes, impedance differs. For example, air has higher impedance compared

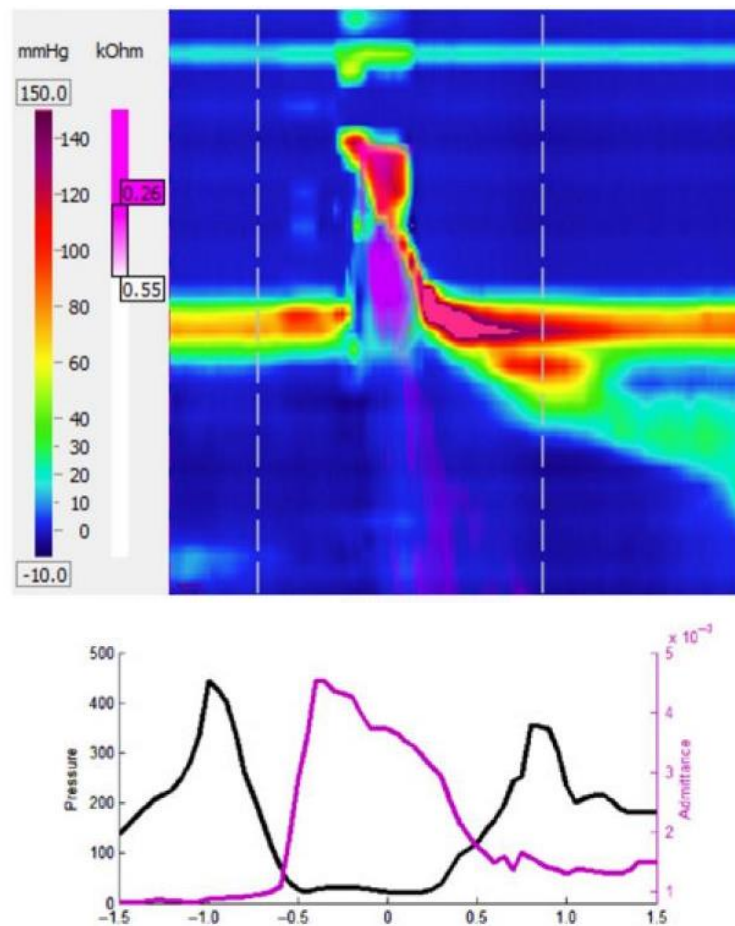
to saline bolus (Kahrilas & Sifrim, 2008; Pandolfino & Kahrilas, 2009). Similar to HRM, HRIM allows for derivation of objective measurements of swallowing including pressure variables, impedance measures, synergistic pressure and impedance measures, and complex measures such as the swallow risk index (Omari, Dejaeger, Tack, Van Beckevoort, & Rommel, 2013).

While the use of impedance was historically more common for evaluation of the oesophagus (Kahrilas & Sifrim, 2008), its use for assessment of pharyngeal swallowing has increased (Omari et al., 2006). Pharyngeal HRIM has been researched in healthy subjects (Cock, Jones, et al., 2016; Omari et al., 2006), patients following stroke (Sung, Lee, Choi, & Kim, 2017), and in patients with diseases, such as Huntington's disease (T. H. Lee, Lee, & Kim, 2012), motor neuron disease (Cock, Besanko, et al., 2016), Parkinson's disease (Rommel, Dejaeger, et al., 2012), multiple sclerosis (Rommel, Dejaeger, et al., 2012), and head and neck cancer (Szczesniak et al., 2015). This technique has been used to evaluate premature bolus spillage (Ferris et al., 2015), aspiration risk (Omari et al., 2013; Omari, Dejaeger, van Beckevoort, Goeleven, Davidson, et al., 2011), and pharyngeal residue (T. H. Lee, Lee, Park, et al., 2014; Omari, Dejaeger, Tack, Vanbeckevoort, & Rommel, 2012; Omari, Dejaeger, Van Beckevoort, Goeleven, De Cock, et al., 2011). Further, the effect of compensatory techniques, such as the supraglottic swallow manoeuvre (Rommel, Selleslagh, et al., 2012), and of swallowing manoeuvres, including Mendelsohn manoeuvre and effortful swallowing (Doeltgen et al., 2017), have been evaluated using pharyngeal HRIM.

#### ***5.4.1. Assessment of UES Function***

For assessment of the UES, measures of pressure were discussed in section 5.3.1. An impedance variable relevant to UES function is called UES nadir impedance (Figure 10). This measure corresponds to the lowest impedance measured at the UES during swallowing. Omari, Ferris, and colleagues (2012) explored whether UES nadir impedance and UES relaxation duration correlate with radiologically assessed diameter of UES opening in healthy subjects and patients with dysphagia. The findings revealed a strong correlation between UES nadir impedance and UES opening diameter with higher nadir impedance associated with decreased UES opening diameter. Conversely, no significant correlation between UES relaxation and UES opening diameter was found. Thus, in the assessment of UES function, nadir impedance may be used to infer maximal opening extent during bolus passage (Cock & Omari, 2017). Similarly, Cock, Besanko, and colleagues (2016) studied UES maximum admittance - the

inverse of UES nadir impedance - in younger and older healthy subjects and in patients with cricopharyngeal bar and motor neuron disease. The study found lower maximum admittance in older compared to younger healthy subjects. Similarly, maximum admittance was decreased



**Figure 10.** High-resolution impedance manometry (HRIM): The image on the top illustrates a swallow in the contour view with the purple colour showing bolus presence (Cock, Jones, et al., 2016)<sup>11</sup>. The black line in the image below depicts the pressure reading at the upper oesophageal sphincter (UES) during a swallow, the purple line the admittance reading (Cock, Besanko, et al., 2016)<sup>12</sup>.

<sup>11</sup> From “Modulation of upper esophageal sphincter (UES) relaxation and opening during volume swallowing” by Cock, Jones, et al. (2016), *Dysphagia*, 32(2), p. 219. Reprinted with permission of Springer Nature.

<sup>12</sup> From “Maximum upper esophageal sphincter (UES) admittance: A non-specific marker of UES dysfunction” by Cock, Besanko, et al. (2016), *Neurogastroenterology & Motility*, 28 (2), p. 228. Reprinted with permission of John Wiley and Sons.

in subjects with cricopharyngeal bar as compared to young healthy adults, as well as in patients with motor neuron disease as compared to healthy subjects of any age. Thus, the authors suggest that UES maximum admittance may be used to determine dysfunction of the UES. The effect of age on UES pressure-flow parameters was explored in healthy participants by Omari and colleagues (2014). Findings suggested a significantly higher UES nadir impedance during bolus flow for liquid and viscous boluses in older subjects than in younger; higher UES nadir impedance corresponds to reduced UES opening diameter. Further, decreased UES intrabolus pressure for liquids was found in older compared to younger subjects.

Omari, Jones, and colleagues (2016) reported on a newly developed method to evaluate UES function based on mechanical states of the UES muscles. Mechanical states, determined based on the association between pressure and admittance, were used to predict EMG activity of the cricopharyngeus and of the submental muscles. The study revealed a strong correlation between pressure-based contraction of the UES muscles and EMG activity at the cricopharyngeus. Further, a high correlation was found between width of UES lumen, based on admittance measurements, and EMG activity of the submental muscles. The authors conclude that mechanical states may be used to predict neural inputs that govern activity of muscles relevant for UES function. These studies suggest a potential of pressure-flow analysis to objectively assess UES function. Yet, reliability data are further necessary to determine the potential of this technology for future research and clinical application.

There are reports of reliability for pressure-flow parameters analysed using automated impedance manometry analysis (AIMplot analysis), a customised MATLAB software programme (Omari, Savilampi, et al., 2016). In this reliability study, swallows of healthy subjects were evaluated by six raters on two occasions (test-retest reliability) with a period of approximately one week between measurement attempts. On each occasion, measurements were derived twice for assessment of intra-rater reliability. Reliability of several UES parameters was reported for the first and second measurement attempt including basal UES pressure (intra-rater ICC: 1.00/1.00, inter-rater ICC: 0.99/0.99, test-retest ICC: 0.94/0.94), post-relaxation peak pressure (intra-rater ICC: 0.93/0.98, inter-rater ICC: 0.96/0.92 test-retest ICC: 0.49/0.47), UES contractile integral (intra-rater ICC: 0.88/0.99, inter-rater ICC: 0.88/0.84, test-retest ICC: 0.67/0.62). While intra- and inter-rater reliability for all UES variables was high, test-retest reliability was more variable across parameters. Further, Cock and Omari (2017) collected normative data ( $n = 50$ ) of pressure-flow variables for different bolus volumes and consistencies using a 3.2 mm catheter. Collected pressure and/or impedance



variables included UES maximum admittance, UES integrated relaxation pressure, UES basal pressure, UES post-deglutitive peak pressure, and UES bolus time. Other than the variables of bolus volume and consistency, further factors such as age or sex should be included in future normative studies.

#### **5.4.2. Methodological Considerations**

There is little research exploring methodological aspects of pharyngeal HRIM. In a recent review regarding application of pharyngeal HRIM, Cock and Omari (2017) delineated how HRIM studies are performed in their centre. Reported methodology included a sitting position of participants, potential application of topical anaesthesia, and a minimum accommodation period of five minutes. Future research is required to investigate the impact of methodological aspects on results. Ferris and colleagues (2018) reported on the effect of the catheter on pressure and bolus flow variables in healthy subjects. For UES parameters, greater UES peak pressure and UES basal pressure, and integrated relaxation pressure was found for a 10-Fr compared to an 8-Fr catheter. Further, UES opening time was significantly decreased when assessed using the larger catheter. The same authors evaluated the effect of bolus volume on HRIM parameters. For the UES, an effect of bolus size was reported for the integrated relaxation pressure, UES maximum admittance, and UES opening time. Similarly, Omari and colleagues (2013) reported on the effect of bolus volume and consistency on pressure flow variables including UES relaxation interval, UES nadir relaxation pressure, median intrabolus pressure and UES resistance in patients with dysphagia. No effect of bolus volume was revealed for any of the UES parameters analysed. Conversely, an increase in UES intrabolus pressure and UES resistance was found for increased bolus viscosity. Based on simultaneous HRIM and videofluoroscopy in healthy subjects ( $n = 10$ ), Omari and colleagues (2006) documented that impedance of the bolus depends on bolus consistency. This study revealed clearer impedance readings for semisolid and solid boluses as compared to liquid boluses. Further research has documented that the intensity of the impedance signal can be increased by use of a saline bolus (Gyawali et al., 2013). There is research required evaluating the effect of salinity percentage on impedance data. Emerging research exploring the impact of methodology on pressure-flow data is critical for optimised interpretation of study findings.

#### **5.4.3. Advantages and Limitations**

In the assessment of UES function, HRIM provides the benefits of objective information about UES pressure and bolus flow through the UES without exposure of radiation. Thus, the use of

HRIM may be particularly beneficial in paediatric populations (Ferris et al., 2016) or for repeated application for diagnostics or as a biofeedback modality. Further, patients with mobility restrictions or those who are bed-bound (Omari et al., 2013) may benefit from this mobile technology. However, compared to videofluoroscopy, HRIM does not provide a gestalt view of swallowing biomechanics as a whole. Further, evaluation of penetration or aspiration is not possible (Kahrilas & Sifrim, 2008) and bolus volume cannot be quantified. As stated previously, analysis of UES function using HRM varies across studies due to the use of individually developed, customised external software. Open-access analysis software has recently become available for analysis of pressure-flow data such as Swallow Gateway (Omari, 2018). These options may contribute to increased clinical applicability and comparability of data across centres. While the use of pharyngeal HRIM in the assessment of UES function is promising, more research is needed to establish normative data, to determine validity and reliability, and to evaluate the effect of methodology on data.

## **6. Objectives and Hypotheses**

### **6.1. Methodological Studies**

#### ***6.1.1. Validity and Reliability of Ultrasound Evaluation of Hyolaryngeal Displacement***

##### *Statement of Problem*

Hyolaryngeal excursion contributes to UES opening during swallowing (Jungheim et al., 2014b); thus, assessing hyolaryngeal displacement is of interest in the evaluation of UES function. Ultrasound has been used to examine hyolaryngeal displacement non-radiologically (Dejaeger & Pelemans, 1996; Kuhl et al., 2003). Several reports suggest that large ultrasound devices provide valid and reliable measurements (Hsiao et al., 2012; Huang et al., 2009). Yet, validity and reliability of newly developed pocket-sized ultrasound systems, that may contribute to increased clinical applicability, are unknown.

##### *Research Questions*

- Do measures of hyolaryngeal excursion acquired using pocket-sized ultrasound systems in healthy subjects achieve sufficient concurrent validity to videofluoroscopic measures?
- Can measures of hyolaryngeal excursion be reliably assessed in healthy subjects using pocket-sized ultrasound systems?

##### *Objectives*

- To validate ultrasound measurements of hyoid excursion and thyrohyoid approximation acquired using a pocket-sized ultrasound instrumentation – the Clarius<sup>TM</sup> system (Clarius, Burnaby CA) – to videofluoroscopic measurements (Study 1: Validity Study).
- To assess intra-, inter-rater, and test-retest reliability of data acquisition of hyoid excursion and thyrohyoid approximation using the Clarius<sup>TM</sup> system (Study 2: Reliability Study).

##### *Hypotheses*

- There will be a strong positive linear relationship between ultrasound and videofluoroscopic measurements of hyoid excursion in healthy adults during swallowing (Study 1: Validity Study)
- A strong positive linear relationship between ultrasound and videofluoroscopic measurements of thyrohyoid approximation will be found in healthy subjects during swallowing (Study 1: Validity Study).

- Using the Clarius™ ultrasound system for assessment of hyoid excursion in healthy adults, good acquisition reliability (ICC > 0.75) will be achieved a) within raters, b) across raters, and c) over time (Study 1: Reliability Study).
- Acquisition reliability of thyrohyoid approximation in healthy subjects will be good a) within raters, b) across raters, and c) over time using Clarius™ ultrasound technology (Study 1: Reliability Study).

### *Significance of Research*

Examination of UES function in the assessment of swallowing is critical, as impairment may heavily impact swallowing safety and efficiency. The use of a pocket-sized ultrasound device in the evaluation of hyolaryngeal excursion may provide information of hyolaryngeal displacement, an individual component of UES function, non-radiologically.

### *Proposed Study (see Chapter 7)*

Healthy participants across different age groups will be seen at two occasions. For investigation of validity, measures of hyoid excursion and thyrohyoid approximation will be concurrently acquired using ultrasound and videofluoroscopy. For assessment of intra- and inter-rater reliability of these measures, three raters will be involved in data collection. To evaluate test-retest reliability, data obtained in the first and second session will be used.

## **6.1.2. Assessment of the UES: A Systematic Review of Pharyngeal HRM/HRIM**

### *Statement of Problem*

HRM provides objective information about pressure patterns in the assessment of the UES at rest and during swallowing (Knigge et al., 2014; J. P. Meyer et al., 2016; Takasaki et al., 2008). Adjunctive impedance informs about bolus flow during pharyngeal swallowing (Omari, Dejaeger, Van Beckevoort, Goeleven, De Cock, et al., 2011). Originally, HRM was developed for the evaluation of oesophageal motility (Clouse & Staiano, 1991); yet, it is increasingly used in the assessment of pharyngeal swallowing (Ghosh et al., 2006; Takasaki et al., 2008). Implementation of pharyngeal HRM with and without adjunctive impedance requires adapted methodology. Methodological aspects of data acquisition and analysis have the potential to substantially impact interpretation of data. The use of pharyngeal HRM/HRIM is in early stages and limited methodological standards are available.

### *Research Question*

What methodology is reported in studies using HRM/HRIM in the assessment of pharyngeal swallowing?

### *Objective*

To provide a summary and appraisal of reported methodology of pharyngeal HRM/HRIM in adult populations.

### *Significance of Research*

A summary and appraisal of existing reported methodology of HRM/HRIM in pharyngeal swallowing assessment will build a foundation for development of optimised protocols. To progress the state of practice of pharyngeal HRM/HRIM, aspects of data acquisition and analysis that need refinement must be identified. Replicability of research is critical to verify published findings; however, for research to be reproducible, detailed report of methodology is required (Laine, Goodman, Griswold, & Sox, 2007). Hence, appraisal of current reporting practice is needed to identify if replicability of studies using pharyngeal HRM/HRIM is warranted.

### *Proposed Study (see Chapter 8)*

A systematic review of reported methodology in studies using pharyngeal HRM/HRIM in adult populations will be conducted. Methodology of data acquisition and data analysis will be analysed and the quality of individual studies, as well as the level of evidence (Howick et al., 2009), will be assessed. Guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, Altman, & The, 2009) and the Assessment for Multiple Systematic Reviews (AMSTAR) (Shea et al., 2007) will be followed for reporting.

## **6.2. Behavioural Study**

### **6.2.1. Behavioural Manipulation of the UES**

#### *Statement of Problem*

Pressure regulation at the UES is critical for airway protection from aspiration of potential reflux and for safe and efficient swallowing (Jungheim et al., 2014b). There is research documenting altered UES pressure during execution of the Mendelsohn manoeuvre and effortful swallowing (Hoffman et al., 2012). These swallowing techniques may alter pharyngeal biomechanics (Logemann, 1998) and swallowing pressure (Huckabee et al., 2005).

However, it is unknown whether pressure at the UES can be manipulated directly, rather than as an indirect effect of alterations of pharyngeal biomechanics or pharyngeal pressure changes.

### *Research Question*

- Can healthy subjects directly modulate pressure at the UES?

### *Objectives*

- To explore if healthy adults can volitionally increase and/or decrease UES resting pressure out of the context of swallowing (Exploratory Study 1).
- To investigate if healthy adults can volitionally prolong pressure-related UES opening duration during swallowing (Exploratory Study 2).

### *Hypotheses*

Healthy adults will be able to volitionally modulate pressure at the UES following biofeedback training. Subjects will:

- increase UES resting pressure without generating pharyngeal pressure in the absence of swallowing (Exploratory Study 1).
- decrease UES resting pressure without generating pharyngeal pressure in the absence of swallowing (Exploratory Study 1).
- prolong pressure related UES opening during swallowing without changing amplitude and temporal characteristics of pharyngeal pressure (Exploratory Study 2).

### *Significance of Research*

This research will contribute to our understanding of the potential for direct pressure modulation of the UES in healthy adults. Greater insight into healthy adults' capability to volitionally control components of pharyngeal swallowing is critical for further development of behavioural treatment options for dysphagic patients. If pressure at the UES could be directly modulated, the specificity of behavioural rehabilitation may be increased. Thus, the project provides a foundation for future studies evaluating purposeful pressure modulation in patient populations with impaired UES pressure regulation.

### *Proposed Study (see Chapter 9)*

For this exploratory research, healthy subjects will perform daily training across a two-week period. For one group, the training goal will be to modulate UES resting pressure in the absence of swallowing (Study 1), for the other group the target will be to prolong pressure related UES opening during saliva swallowing (Study 2). HRM will be used to support performance as a

visual biofeedback modality. The ability to manipulate UES pressure will be assessed prior to training and as an effect of one and two weeks of training. Additionally, participants will complete a follow-up assessment after a training break of two weeks to evaluate retention. To assess whether participants have the potential to manipulate UES pressure without generating pharyngeal pressure at rest or altering pharyngeal pressure during swallowing, pressure in the pharynx will also be analysed.

## **Part II: METHODOLOGICAL STUDIES**



## **7. Validity and Reliability of Ultrasound Evaluation of Hyolaryngeal Displacement**

### **7.1. Introduction**

Effective bolus passage through the UES requires a coordinated interaction between relaxation of the cricopharyngeus and traction forces of the hyolaryngeal complex acting on the UES to enable opening (Easterling & Shaker, 2013; Jungheim et al., 2014b; Lang & Shaker, 2000). Thus, examination of hyolaryngeal excursion is an event of interest in UES assessment. For instrumental assessment of hyolaryngeal displacement, videofluoroscopy is commonly used (Leonard et al., 2000; Sia et al., 2012; Thompson et al., 2014). Videofluoroscopic imaging exposes patients to radiation; hence, its use for prolonged examinations, repeated testing and application in vulnerable patient populations such as paediatrics is limited (Rugiu, 2007). Further, access to a videofluoroscopy suite may be challenging for patients who are critically ill, restricted in their mobility or for those living in rural areas (Rugiu, 2007). Compared to videofluoroscopy, the use of ultrasound yields benefits as a radiation-free, non-invasive imaging modality (Hsiao et al., 2012). Its use for assessment of hyoid excursion (Dejaeger & Pelemans, 1996; Yabunaka et al., 2011) and thyrohyoid approximation (Huang et al., 2009; Kuhl et al., 2003) has been documented in the literature.

While ultrasound imaging has been utilised in swallowing research for many years (Skolnick, Zagzebski, & Watkin, 1975; Stevens, 1978), its application has not translated into common clinical practice. This may be due, in part, to the costs and the cumbersome nature of most large ultrasound devices. With technical progress, small, portable ultrasound systems have been developed. Such pocket-sized systems could be useful for repeated evaluation of hyolaryngeal displacement in paediatrics, for application in patients who are not able to mobilise out of bed and thus cannot be transferred to a videofluoroscopy suite or for those living in rural communities with challenging access to videofluoroscopy (Rugiu, 2007). Evaluation of validity and reliability are essential prior to implementation of medical instrumentation into clinical routine (Portney & Watkins, 2009). Validity reflects whether instrumentation measures what it proposes to measure (Kimberlin & Winterstein, 2008; Portney & Watkins, 2009). Reliability provides information about how consistent measurements can be derived with a given method. For validation of ultrasound, a comparison of ultrasound against videofluoroscopy is appropriate as its use for visualisation of swallowing biomechanics is undisputed. However, it is important to acknowledge that even if some have termed this

technology the gold-standard for instrumental swallowing examination (Rugiu, 2007), also for videofluoroscopy validity and reliability are emerging.

In the literature, there is evidence of validity when measurements of hyolaryngeal excursion derived from established ultrasound instrumentation and from videofluoroscopy are compared. Two studies have documented a strong correlation between ultrasound and videofluoroscopic measurements of hyoid excursion in dysphagic patients (Y.-C. Chen et al., 2017; Hsiao et al., 2012), while one study reported no significant difference between ultrasound and radiographic measurements of thyrohyoid approximation in dysphagic subjects (Huang et al., 2009). Further, good intra-rater and moderate to good inter-rater reliability, according to the criteria published by Portney and Watkins (2009), has been reported for ultrasound assessment of hyoid excursion in healthy adults (Hsiao et al., 2012; Macrae et al., 2012) and in patients with dysphagia (Y.-C. Chen et al., 2017). Good intra- and inter-rater reliability has been documented for thyrohyoid approximation in healthy adults (Huang et al., 2009). Notably, reliability documented by Hsiao and colleagues (2012) and Huang and colleagues (2009) included the entire process of data acquisition comprising scanning, image selection from the video for measurement, and measurement. Conversely, reliability in the study by Macrae and colleagues (2012) included image selection and measurement, in the study by Chen and colleagues (2017) only measurement reliability was explored. However, to translate ultrasound to clinical swallowing examination, good intra- and inter-rater reliability of the entire process of data acquisition is required. Additionally, good test-retest reliability is necessary for repeated testing; yet, there is a lack of data regarding reliability over time.

This research programme consists of two studies. The first study investigated if valid measurements of hyoid excursion and thyrohyoid approximation could be derived from a pocket-sized ultrasound system – the Clarius™ system (Clarius, Burnaby CA) – when compared to measures acquired with videofluoroscopy. For facilitated interpretation of validity, the second study examined intra-, inter-rater, and test-retest reliability of hyoid excursion and thyrohyoid approximation acquired with the Clarius™ ultrasound. Since assessment of the UES is a key focus of this thesis, evaluating reliability of hyoid excursion and thyrohyoid approximation was of significant interest. A concurrent study that studied tongue thickness and CSA of the floor of mouth muscles using Clarius™ ultrasound was being conducted in the same laboratory by other researchers. Therefore, this research also reports reliability of these two measures. To replicate clinical application, reliability was examined for

the entire process of data acquisition including the process of scanning, online image selection, and online measurement. Based on the findings, further exploration of two types of offline measurement reliability was conducted to clarify how different components of data acquisition impacted reliability: ‘Video measurement reliability’ incorporated both image selection from the video and measurement, whereas ‘image measurement reliability’ evaluated only measurement of pre-selected images.

It was hypothesised that there would be a positive, strong linear relationship between measurements of hyoid excursion and thyrohyoid approximation derived from ultrasound and videofluoroscopy. Intra-, inter-rater and test-retest reliability of data acquisition would be good ( $ICC > 0.75$ ) for hyoid excursion and for thyrohyoid approximation.

## **7.2. Study 1: Validity Study**

### **7.2.1. Materials and Methods**

#### *7.2.1.1. Participants*

A total of 20 healthy adults were recruited with five participants in each of the following age groups: 20 - 39, 40 - 59, 60 - 79, and 80+ years. Female and male participants were equally represented. Exclusion criteria included history of swallowing impairment or current swallowing difficulty, neurological or muscular disease, head and neck tumour or anatomical abnormalities of the head and neck region, drugs, which might have an impact on swallowing, or pregnancy. Participants were recruited via advertisements, community talks, and an in-house volunteer data base. Approval for this research was obtained by the Human Ethics Committee of the University of Canterbury (HEC 2017/20). Participants received verbal and written information about the research and provided informed consent prior to data collection. Participant demographics were collected, including ethnicity, sex, date of birth, height, weight, and handedness.

#### *7.2.1.2. Instrumentation*

A curvilinear Clarius™ scanner (frequency range: 2 - 6 MHz, depth: 3 - 30 cm) was used for ultrasound high-resolution live imaging (Figure 11). The Clarius™ application software was installed on an iPad (screen size 20 cm x 15 cm) to which the scanners connected wirelessly. Recordings were visualised on the iPad with a frame rate of 20 frames per second. Videoclips and individual images were saved for derivation of measures. A web-based portal (Clarius™

Cloud) was used for storage of data. For videofluoroscopic imaging, a GE Fluorostar Fluoroscope with a frame rate of 25 frames per second was used.



**Figure 11.** Pocket-sized curvilinear Clarius™ ultrasound scanner.

#### 7.2.1.3. *Study Preparation*

For optimal methodological use of this new technology, imaging settings with varying features such as the focal point were trialled and compared by the key researchers (Rater 1, Rater 2, Rater 3). Following advice from experts in the field of ultrasound and experiences of the research team, the manufacturer adjusted existing settings of Clarius™ to optimise the use of this instrumentation for the swallowing measures involved in this study. Specifically, a setting was developed to maximise image clarity of superficial muscles using the curvilinear transducer.

The key researchers met regularly over a period of several months during project development to discuss and standardise scanning methods and measurement characteristics. Measurements were based on existing data from the literature. Prior to initiation of data collection, consensus ratings between raters were acquired for data acquisition and measurement. Subsequently, the researchers agreed on scanning and measurement techniques. A written document was established in preparation for the Validity and Reliability Study. This document included clear measurement descriptions and example images and served as a practical guideline for the raters (*Appendix B.2*). Thus, training was consensus based, yet non-standardised.

#### 7.2.1.4. *Procedure*

In total, participants attended two sessions for this research project. Concurrent ultrasound and videofluoroscopic imaging of hyoid excursion and thyrohyoid approximation was performed in the first session (Validity Study); the second session served for assessment of reliability only (Reliability Study).

##### 7.2.1.4.1. *Setting*

Subjects were seated in a chair placed within the C-arm of the fluoroscope; a towel was placed at the back of the participant's neck to ensure stable head position. A calibration disc of known size (1.97 cm in diameter) was taped laterally to the participant's face for post-hoc measurement. For radiation protection, participants and researchers wore lead aprons or skirts. Additionally, the researcher wore a leaded sleeve, gloves and glasses as ultrasound acquisition required close proximity to the beam during radiographic imaging due to manual ultrasound transducer placement. The time of radiation exposure was limited to less than three minutes.

##### 7.2.1.4.2. *Order and Number of Measures*

Order of data acquisition was randomised between hyoid excursion and thyrohyoid approximation. To limit radiation exposure, participants performed each measure once only per bolus consistency.

##### 7.2.1.4.3. *Bolus*

Data acquisition of hyoid excursion and thyrohyoid approximation involved swallowing of saliva, 5 mL water, and 5 mL apple sauce (brand Wattie's). Solid boluses were not included into the protocol as oral movements for bolus formation and mastication would not allow for stable transducer placement. Different consistencies were tested to reflect common clinical practice and to account for potential impact of bolus consistency on validity. A rather small 5 mL bolus was selected as this is a commonly reported quantity in reliability studies using ultrasound for assessment of hyolaryngeal excursion (Y.-C. Chen et al., 2017; Hsiao et al., 2012); thus, the use of the same bolus size increases the comparability of the study results to published reliability data. Further, this bolus size was selected to encourage one discrete swallow per bolus that may contribute to facilitated assessment. Quantities were measured with a syringe for volume control. Liquid boluses were offered in a 20 mL plastic cup, pureed boluses with a spoon. The order in which different bolus types were presented (saliva, water,

puree) was kept consistent across participants and sessions to reflect the sequence routinely followed in clinical practice. Bolus administration was performed by the participants.

#### *7.2.1.4.4. Instruction*

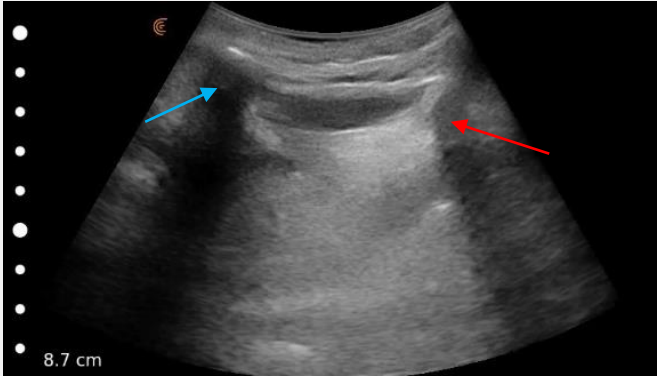
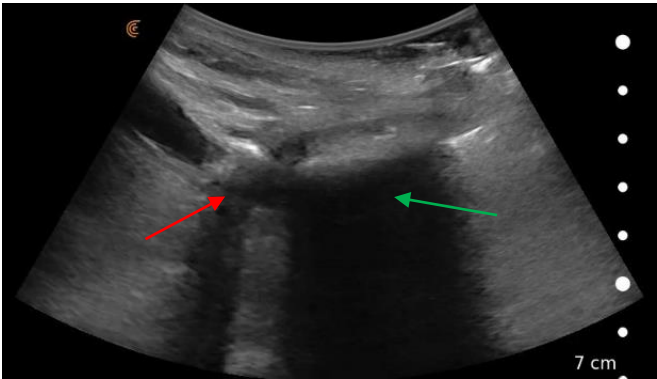
Participants were instructed to hold a bolus in the mouth. Once the scanner was placed, they were asked to swallow as naturally as possible, whenever ready.

#### *7.2.1.4.5. Recording*

*Ultrasound:* For ultrasound data acquisition, the probe face was coated in aquasonic transmission gel for acoustic coupling prior to manual placement of the scanner on the participant's skin surface. The scanner position was maintained throughout data acquisition. Pressure against the skin was kept minimal to avoid distorting measurement through external pressure (Stone, 2005). Manual rather than fixed transducer placement was selected as there is insufficient data to suggest improvements in measurement accuracy by use of transducer stabilisation (Perry et al., 2016). Further, hand-held transducer placement has an increased potential for clinical applicability. Brightness mode, also referred to as 2D mode, was applied for two-dimensional grayscale imaging. The Clarius<sup>TM</sup> device uses pre-set exam types, with set characteristics such as scanning depth or gain. Specific pre-settings were selected per measure, as specified in Table 3. If necessary, the depth, gain, and display brightness were manually accommodated per measure and participant to achieve best image quality. Consistent imaging quality was assured by the researcher through visual monitoring. Each swallowing event was recorded as an individual video-clip of 20 s. Measure specific recording information is provided in Table 3.

*Videofluoroscopy:* For videofluoroscopic examination, a low dose continuous cine mode with a frame rate of 25 frames per second was selected. At least one snapshot was taken prior to video recording to ensure that key features such as the hyoid and thyroid cartilage were distinctly visible in the frame and that the image encompassed the following anatomical structures: mandible (anteriorly), nasal cavity (superiorly), cervical spine (posteriorly), proximal oesophagus and trachea (inferiorly).

**Table 3.** Ultrasound recording: Measurement specific information

Measure	Scanner; Name of pre-setting	Imaging method	
Hyoid excursion	Curvilinear; Clarius™ ‘Abdomen’ pre-setting (depth 7 – 10 cm, frequency: 4 MHz, single focus, dynamic range: 52 dB)	A sagittal sonogram was performed with the scanner positioned at right angles to the floor of mouth muscles. The scanner was placed midline, capturing the acoustic shadow of the mandible on one side (blue arrow) and on the other side the acoustic shadow of the hyoid (red arrow) (Macrae et al., 2012). Inferiorly, the surface of the tongue was visible.	
Thyrohyoid approximation	Curvilinear; Clarius™ ‘Superficial’ pre-setting (depth 1 - 7 cm, frequency: 5 MHz, dual focus, dynamic range: 65 dB)	For performance of the sagittal sonogram, the scanner was positioned midline, superposing the thyrohyoid muscle or slightly off midline to ensure sufficient skin contact, to visualise key features including the acoustic shadow of the hyoid on one side (red arrow), and the acoustic shadow of the thyroid cartilage on the other side (green arrow) (Kuhl et al., 2003).	

#### 7.2.1.5. Data Extraction

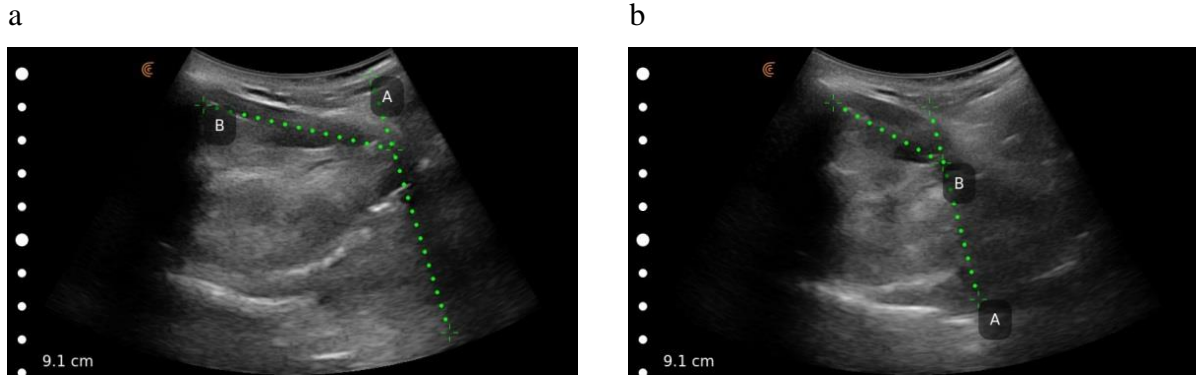
*Ultrasound:* For extraction of ultrasound data, specific images for measurement were selected on the iPad by navigating through the recorded video. A straight-line tool was selected for measurement and placed by use of a touch pen or fingertip. Image selection and measurement were performed after each swallow. If a subject swallowed twice per bolus, the primary swallow, as determined with videofluoroscopy, was measured. Following completed data extraction of a session, all collected ultrasound videos and images were uploaded to the Clarius™ Cloud for storage; images were saved with and without displayed measurement cursors. Measurements were written on a Word document prior to export to an Excel file. Correct data transfer from Word to Excel was ensured by a second person by visual comparison of data in both documents.

##### 7.2.1.5.1. Hyoid Excursion (Ultrasound)

*Image selection:* For data extraction of hyoid excursion, two images were selected, one with the hyoid at rest and one representing the peak of hyoid displacement. The rest image was selected post-swallow rather than pre-swallow, as preparatory hyoid movement often occurs before swallowing and bolus containment may alter rest position of the hyoid. The peak position image was defined as the one showing the smallest distance between shadow cast by the hyoid and shadow cast by the mental spine.

*Measurement:* Two straight lines were used for measurement (Figure 12). First, the best fit line was drawn along the anterior border of the shadow cast by the hyoid (Line A). For the second line (Line B), one calliper was placed at the posterior border of the onset of the shadow created by the mental spine. The second calliper was placed at the intersection point with the best fit line at the onset of the shadow cast by the hyoid. The extent which the hyoid travels was expressed as a percentage of the distance at maximal displacement from rest (Macrae et al., 2012). Percentage change, rather than absolute change, was calculated as relative change allows comparison across individuals. Further, previous research reported higher reliability for relative than for absolute displacement (Macrae et al., 2012). This measurement technique was based on reports by Macrae and colleagues (2012) with the difference that in this study the line of best fit was additionally used to facilitate identification of measurement points.



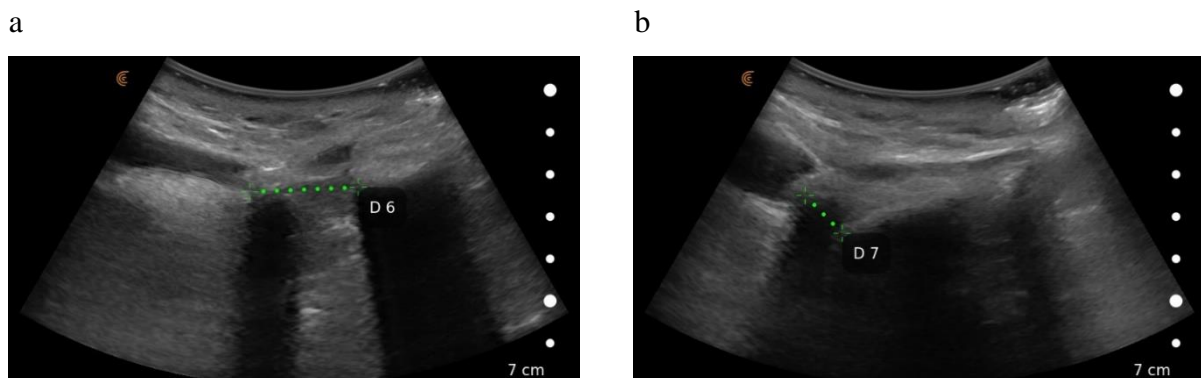


**Figure 12.** Sonogram of the hyoid at rest position (a), and at maximal displacement (b). The shadow on the left of the images is cast by the mandible, the shadow at the right is cast by the hyoid. The depth scale is shown on the left lower corner of the window.

#### 7.2.1.5.2. Thyrohyoid Approximation (Ultrasound)

*Image selection:* Data extraction of thyrohyoid approximation involved selection of two images from the videos, showing hyoid and thyroid cartilage at rest and with the two structures maximally approximated. The rest image was again selected post-swallow.

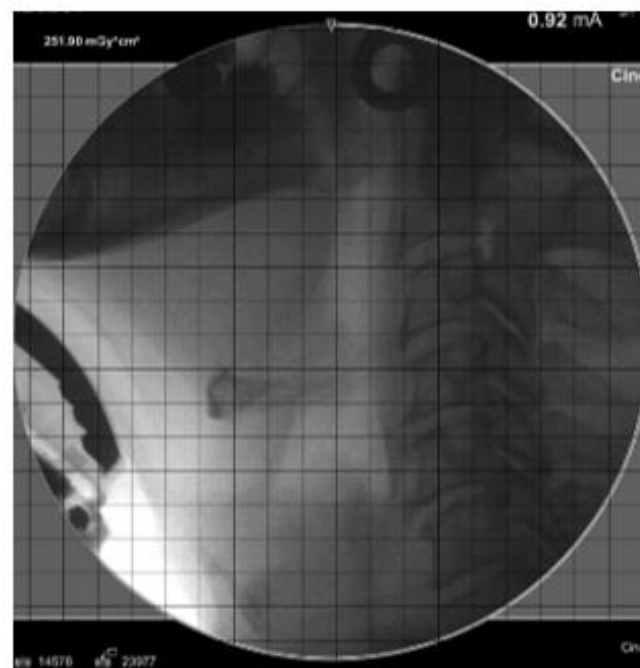
*Measurement:* For measurement, one single straight line (Line D) was used to measure the distance between the upper border of the thyroid cartilage and the hyoid (Figure 13) (Huang et al., 2009; Kuhl et al., 2003). One calliper was placed at the beginning of the anterior border of the shadow of the hyoid or at the opacity representing the hyoid. Of the two marks, the one that was consistently visible in both images was selected. The other calliper was placed at either the onset of the shadow cast by the thyroid cartilage or at the bright opacity at the superior border of the thyroid cartilage. Of the two points, the one that was visible in both images was



**Figure 13.** Sonogram of the distance between hyoid and thyroid cartilage at rest (a), and at maximal approximation (b). The shadow on the left of the windows is cast by the hyoid, the one on the right by the thyroid cartilage.

selected. Thyrohyoid approximation was expressed as a percentage of the distance between thyroid cartilage and hyoid at maximal approximation from rest (Huang et al., 2009; Kuhl et al., 2003). This measurement technique was based on images published by Huang and colleagues (2009); written descriptions were not provided in this manuscript.

*Videofluoroscopy:* For extraction of videofluoroscopic data, recordings were exported from the fluoroscope to a computer. Using ImageJ software, a grid was superimposed on the recordings for facilitated identification of the target measurement images (Figure 14).



**Figure 14.** Videofluoroscopy: Grid superimposed to the radiographic image.

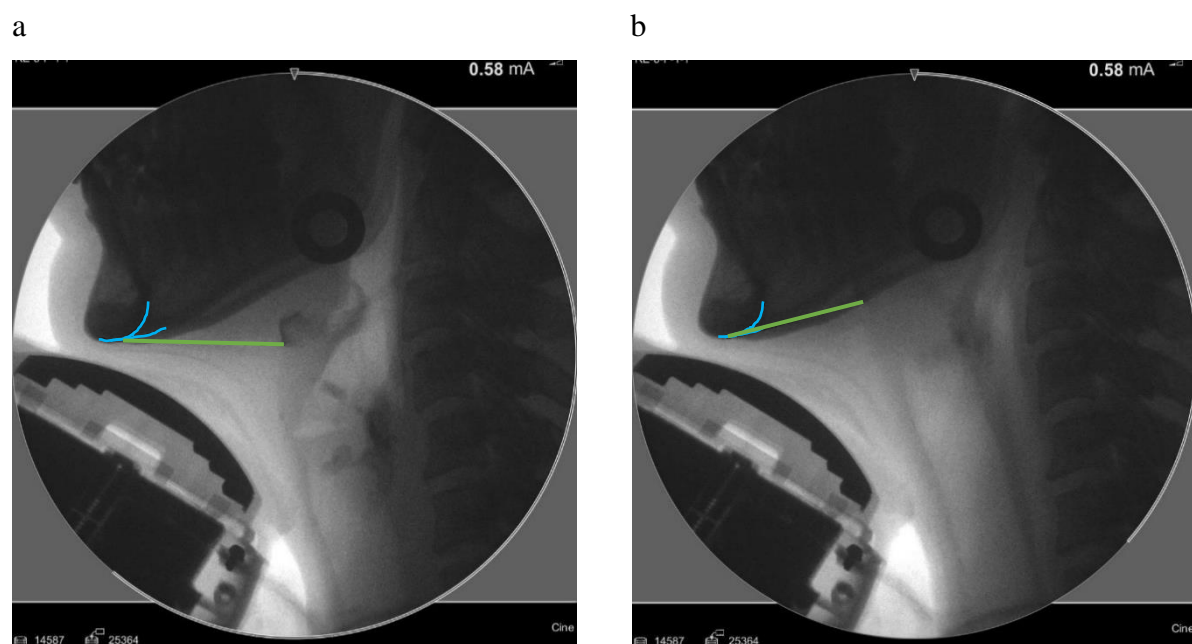
Selected images were saved as individual images. In the event that a primary and a clearance swallow was recorded, the primary swallow was measured. If target structures were not distinctly visible, brightness and contrast modification options of ImageJ were used for facilitated selection of the measurement points. Calibration of each image was required prior to measurement. The default method for calibration using ImageJ requires placing a straight line along the imaged calibration object to allow for automated calibration (Leonard et al., 2000). However, using this method, considerable calibration errors were revealed in this study. The reason for these errors is likely twofold. First, in the event that the X-rays did not hit the circle calibration object in a 90° angle, the circle object appeared as an oval on the videofluoroscopic image. Correct calibration is still possible if the biggest diameter of the oval is used; however, it proved to be difficult to visually determine the biggest diameter. Secondly, it was challenging to place the calibration line exactly through the centre of the disc which is

critical for correct calibration. To minimise calibration error, manual calibration was performed by tracing around the disc outline with a circle measurement tool; the circle was placed such to fit the maximal diameter of the calibration disc. No image rotation to correct potential head movements during swallowing was applied as the measurement methods on videofluoroscopy were matched to the ones on ultrasound.

#### 7.2.1.5.3. Hyoid Excursion (Videofluoroscopy)

*Image selection:* For validation purpose, measurement methods of the radiographic images were approximated to those for ultrasound. Data extraction of hyoid excursion involved selection of two still images, one depicting the hyoid at rest and one at maximal anterior displacement. The rest image was selected post-swallow.

*Measurement:* For measurement, the following two points were used (Figure 15): the inferior-anterior part of the hyoid and, according to the method described by Thompson and colleagues (2014), the mandibular prominence “where the inferior line of the body of the mandible meets the symphyseal outline of the mandible” (p. 6). The percentage change from the position at rest and at maximal displacement was calculated.

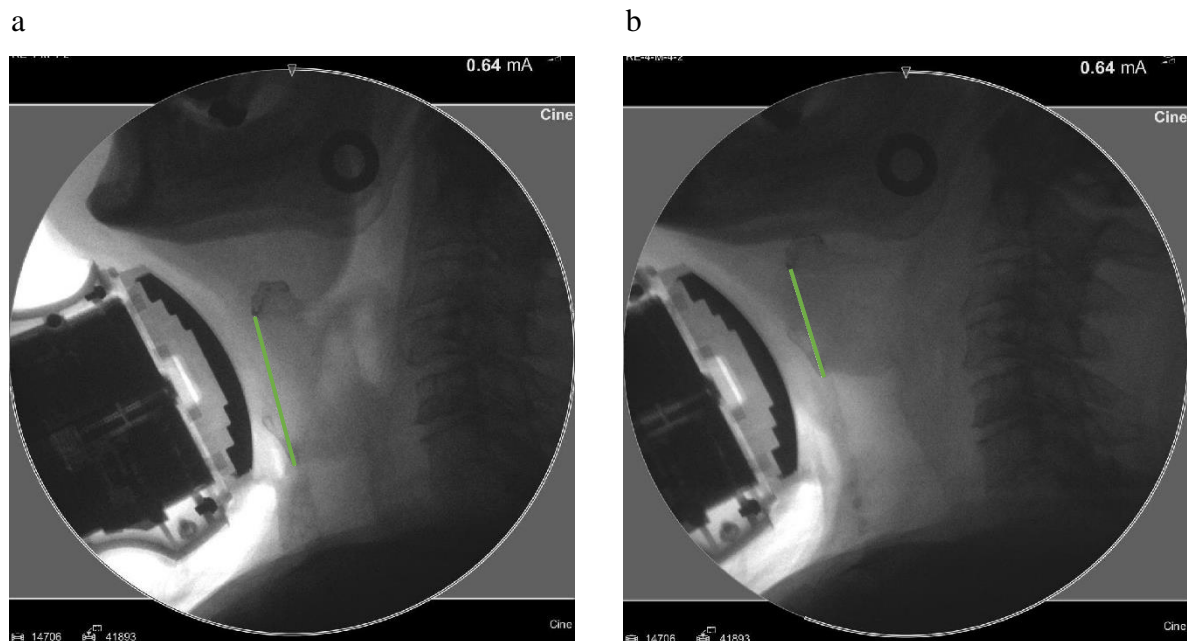


**Figure 15.** Measurement lines (green) for assessment of the distance from hyoid to mandible at rest (a), and at maximal hyoid displacement (b). The blue drawings were used to define the measurement point at the mandibular prominence.

#### 7.2.1.5.4. Thyrohyoid Excursion (Videofluoroscopy)

*Image selection:* For data extraction of thyrohyoid approximation, two still images were selected, one depicting the hyoid and thyroid cartilages at rest and one at maximal approximation of the two structures. The rest image was selected post-swallow.

*Measurement:* The anterior-inferior aspect of the hyoid and a consistent landmark at the anterior border of the inferior end of the thyroid cartilage (Leonard et al., 2000) or cricoid cartilage served as measurement points for calculation of percentage approximation from rest (Figure 16). As opposed to ultrasound, the inferior rather than the superior border of the thyroid cartilage was chosen for two reasons. First, the upper border was often not sufficiently distinct visible for measurement. This may be explained by the fact that the two thyroid laminae are not fused above the thyroid notch; differences across individuals may be due to variable ossification of the cartilage (Dang-Tran et al., 2010). Secondly, even if it was visible, the distance between upper border of the thyroid cartilage and hyoid was minimal given the lateral view using videofluoroscopy. In some cases, the upper border of the thyroid cartilage superimposed the hyoid at maximal excursion; hence, calculation of percentage approximation would yield more than 100%. In ultrasound, this issue occurred less frequently since the structures were imaged anteriorly and with a curvilinear transducer that may allow visualisation of both structures at the peak of the swallow by distortion of the image.



**Figure 16.** Measurement lines (green) depicting the distance between hyoid and thyroid cartilage at rest (a), and at maximal approximation (b).

#### 7.2.1.6. *Data Analysis*

Means and standard deviations (SD) were calculated for both measures and both instrumentation across participants. Reliability of ultrasound measurements is covered in the Reliability Study (7.3.1.7). For intra-rater reliability assessment of videofluoroscopic measurements, 20% of the videofluoroscopic recordings of hyoid excursion (24 recordings) and 20% of the recordings of thyrohyoid approximation (24 recordings) were selected by randomisation. A separate 20% of the data of each measure were randomly selected for evaluation of inter-rater reliability. Reliability assessment included image selection and measurement. Mixed-effects analyses (Bates, Mächler, Bolker, & Walker, 2015) were performed using R software (R Core Team, 2016) to calculate ICC estimates and their 95% confidence interval. Assessment of intra-rater reliability was based on a two-way mixed effects model (ICC[3,1]), inter-rater reliability was calculated using a two-way random effects model (ICC[2,1]) for agreement of single measures. A likelihood ratio test was used to test for a potential bolus effect: the full model which included bolus as a fixed effect was compared the reduced model that did not contain bolus as a fixed effect. If there was a significant bolus effect, analysis using the full model was continued to remove variability due to bolus consistency. If there was no bolus effect, the reduced model was used. Residual versus fitted plots were visually inspected to identify potential deviation from homoscedasticity patterns; quantile-quantile plots (Q-Q plots) of the residuals were visually inspected to ensure normality.

##### 7.2.1.6.1. *Correlation*

For assessment of validity, a Pearson's correlation coefficient ( $r$ ) was calculated to determine strength and direction of a linear relationship between ultrasound and videofluoroscopic measurements (Udovičić, Baždarić, Bilić-Zulle, & Petrovečki, 2007). To analyse the strength of the evidence for a relationship, a  $p$ -value was calculated. Analyses were performed using R software (R Core Team, 2017). First, the assumptions of a Pearson's correlation analysis were checked. Sample data of ultrasound and videofluoroscopic measures were plotted using scatter plots to assess whether the relation between the two variables was linear. Residual versus fitted plots were additionally used to assess linearity and to detect any variance patterns of the residuals. To evaluate normality of the data, Q-Q plots were visually inspected, and a Shapiro-Wilk's test was conducted. A  $p$ -value of  $\leq .05$  was considered significant. Pearson's correlation coefficient was calculated if the assumptions were met. If the assumption were violated, a non-parametric Kendall's correlation coefficient ( $\tau$ ) was calculated. For interpretation, the guidelines depicted in Table 4 were used (Allen, 2017).

**Table 4.** Guidelines for interpreting Pearson’s correlation coefficients (Allen, 2017)

Positive relationship	Negative relationship	Strength of relationship
< 0.19	< - 0.19	Negligible
0.20 to 0.39	- 0.20 to - 0.39	Weak
0.40 to 0.59	- 0.40 to - 0.59	Fair
0.60 to 0.79	- 0.60 to - 0.79	Moderate
0.80 to 1.00	- 0.80 to - 1.00	Strong

#### 7.2.1.6.2. Agreement

Post-hoc agreement analyses were performed to quantify differences in measurements across instruments considering that measurement methods differed across the two imaging modalities (Giavarina, 2015). Limits of agreement were calculated to quantify the range within 95% of the differences between the two methods are estimated to lie for most subjects (Bartlett & Frost, 2008; Bland & Altman, 1995; Giavarina, 2015). Bias between ultrasound and videofluoroscopic measurements was defined, as suggested in the literature, if the line of equality (zero on the Y-axis) does not lie within the 95% confidence interval of the mean difference (Bartlett & Frost, 2008; Giavarina, 2015). First, it was checked if the assumption of normality of the differences between paired videofluoroscopic and ultrasound measurements was satisfied for calculation of limits of agreement. Q-Q plots were visually inspected and statistical analyses using the Shapiro-Wilk test were performed; a  $p$ -value of  $\leq .05$  was considered significant. If the assumption was met, limits of agreement were calculated based on the mean of the difference of paired ultrasound and videofluoroscopic measures  $\pm 1.96$  times the standard deviation of the differences. As the limits of agreement are estimates based on a sample, 95% confidence intervals were calculated to express the uncertainty of these estimates (Giavarina, 2015). If the assumption was violated, analysis was not further continued. To visualise agreement between measures derived from ultrasound and videofluoroscopy, differences between paired measurements derived from the two instruments were plotted against the mean of the paired measurements (Bland-Altman plot) (Altman & Bland, 1983).

#### 7.2.2. Results

Ten females and 10 males were recruited with five subjects in each targeted age group. Details of demographics are depicted in *Appendix B1*. All participants completed the full protocol, although slight amendments of the protocol were required during the study. For the first

participant, videofluoroscopic imaging was conducted at the completion of the session. Radiographic imaging was shifted to the middle of the session for all following participants because of increasing technical issues with the ultrasound scanner batteries during the course of the session. This change was implemented to reduce the risk of missing data, which would require repeated radiographic imaging. The criteria for data extraction of thyrohyoid approximation was slightly refined approximately one month after start of data collection. Initially, two lines were applied for measurement from which one line was used to draw the best fit line along the shadow of the hyoid. As the hyoid shadow was not consistently clear across selected images, the decision was made to allow the rater choose whether to use the best fit line or to independently draw a single line between hyoid and thyrohyoid cartilage. Further, for measurement of thyrohyoid approximation, one calliper was initially placed at the onset of the shadow of the hyoid. Given great inter-individual variability as to how consistently the hyoid shadow was visible in both measurement images, this criterion was relaxed to allow greater accommodation for different images. The new criterion was to place one calliper either at the beginning of the anterior border of the shadow of the hyoid if consistently visible in both measurement images or at the hyoid opacity if consistently visible in both images.

Means and standard deviations for both measures and bolus consistencies derived from ultrasound and videofluoroscopy are reported in Table 5. These statistics were based on all acquired measurements. Reliability of ultrasound measurement is presented in section 7.3.2.1. For reliability of videofluoroscopic data extraction, measures of thyrohyoid approximation were omitted from analysis according to the criteria used for data exclusion for validity analysis. Images with insufficient visibility of the thyroid cartilage for measurement ( $n = 5$  for intra-rater reliability;  $n = 3$  for inter-rater reliability) were excluded and images with incomplete visualisation of the calibration disc ( $n = 1$  for intra-rater reliability). The assumptions of normality and of homoscedasticity of the residuals were met except for inter-rater reliability of thyrohyoid approximation. There was no bolus effect for intra- and inter-rater reliability of hyoid excursion and for inter-rater reliability of thyrohyoid approximation, while a bolus effect was found in the model used for intra-rater reliability of thyrohyoid approximation ( $p = .05$ ); thus, bolus was included as a fixed effect into the model. As illustrated in Table 6, the findings indicate good intra-rater reliability for videofluoroscopic data extraction of hyoid excursion and thyrohyoid approximation according to the interpretation criteria published by Portney and Watkins (2009). Inter-rater reliability was moderate for hyoid excursion. The assumptions for analysis of inter-rater reliability of thyrohyoid approximation were not met; thus, results should be interpreted with caution.

**Table 5.** Videofluoroscopic and ultrasound measures: Mean and standard deviation

Measure	Bolus	Mean (SD) for videofluoroscopy	Mean (SD) for ultrasound
Hyoid excursion	Dry	24.31 percentage change (7.23)	26.24 percentage change (5.68)
	Liquid	25.73 percentage change (5.82)	29.63 percentage change (7.22)
	Puree	26.94 percentage change (5.94)	27.61 percentage change (8.79)
Thyrohyoid approximation	Dry	32.08 percentage change (11.51)	43.57 percentage change (5.68)
	Liquid	34.35 percentage change (11.63)	37.48 percentage change (7.22)
	Puree	32.49 percentage change (12.25)	41.08 percentage change (14.81)

*Note.* SD = standard deviation

**Table 6.** Intra-, Inter-rater reliability for videofluoroscopic measures

Measure	Bolus	Intra-rater ICC (95% CI)	Inter-rater ICC (95% CI)
Hyoid excursion	Dry, liquid, puree	.94 (.78, .98)	.74 (.29, .91)
Thyrohyoid approximation	Dry, liquid, puree	.93 (.72, .99)	[.34] (.00, .76)

*Note.* ICC = intraclass correlation coefficient, CI = confidence interval, [] = assumption for reliability analysis not met

#### 7.2.2.1. Correlation

Videofluoroscopic data were excluded, as described previously, if the visibility of the calibration coin or of target structures were insufficient for measurement purposes. No data was excluded based on the reliability findings. Out of 60 acquired measurements for hyoid excursion, 58 were analysed. For thyrohyoid approximation, 44 of the 60 measurements were considered for analysis. All ultrasound measures were included into analysis. The assumptions for Pearson's correlation analysis were met for hyoid excursion and thyrohyoid approximation



during dry and liquid swallowing. The assumptions were violated for both measures during puree swallowing. As depicted in Table 7, there was evidence of an association between ultrasound and videofluoroscopic measurements of hyoid excursion during dry and liquid swallowing; the positive correlation was strong for dry swallowing, and moderate for liquid swallowing. For puree swallowing, no significant evidence for an association was found. There was no significant evidence for an association between ultrasound and videofluoroscopic measurements of thyrohyoid approximation during swallowing of any analysed bolus types.

**Table 7.** Correlation between ultrasound and videofluoroscopic measurements of hyoid excursion and thyrohyoid approximation

Measure	Bolus	Correlation coefficient, <i>p</i> -value
Hyoid excursion	Dry	$r = 0.79, p \leq .001^*$
	Liquid	$r = 0.67, p \leq .002^*$
	Puree	$\tau = 0.27, p = .11$
Thyrohyoid approximation	Dry	$r = 0.36, p = .20$
	Liquid	$r = 0.27, p = .35$
	Puree	$\tau = 0.16, p = .44$

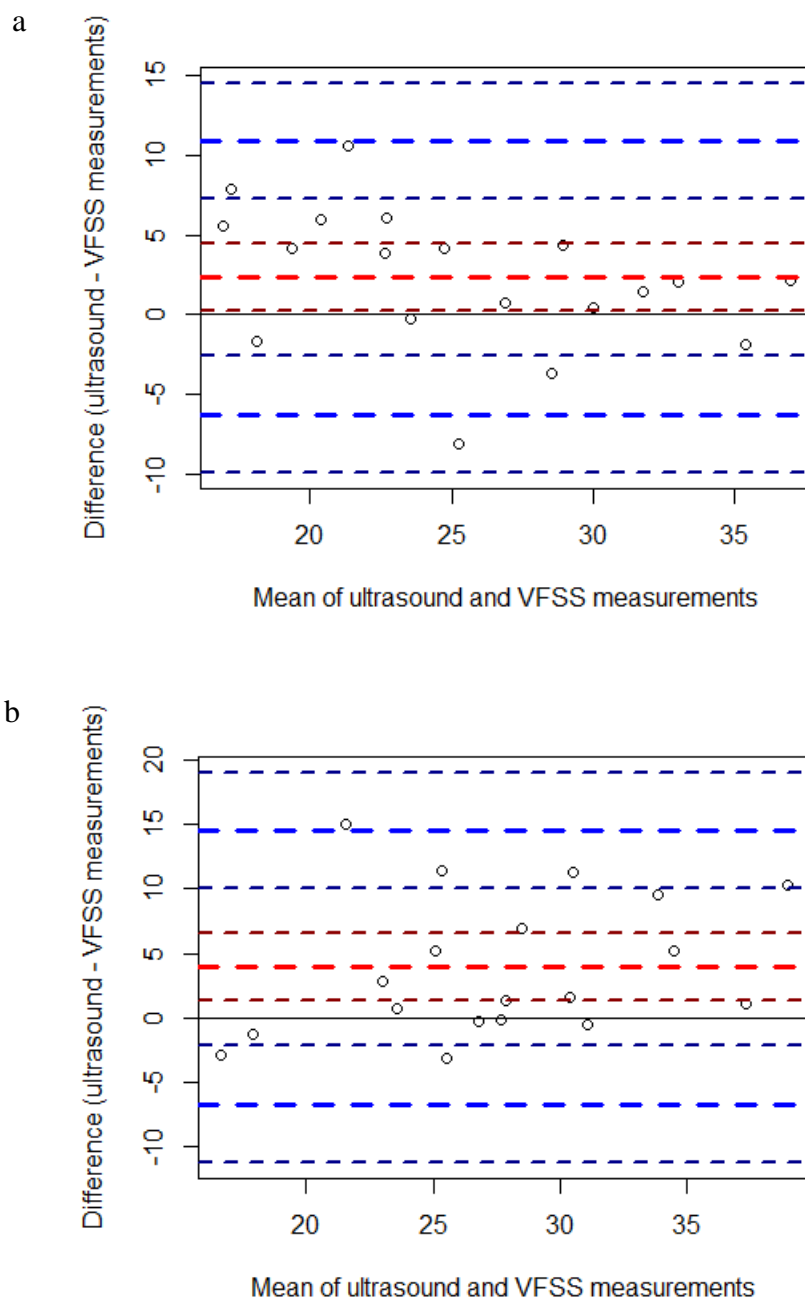
Note. \*significant at  $p \leq .05$

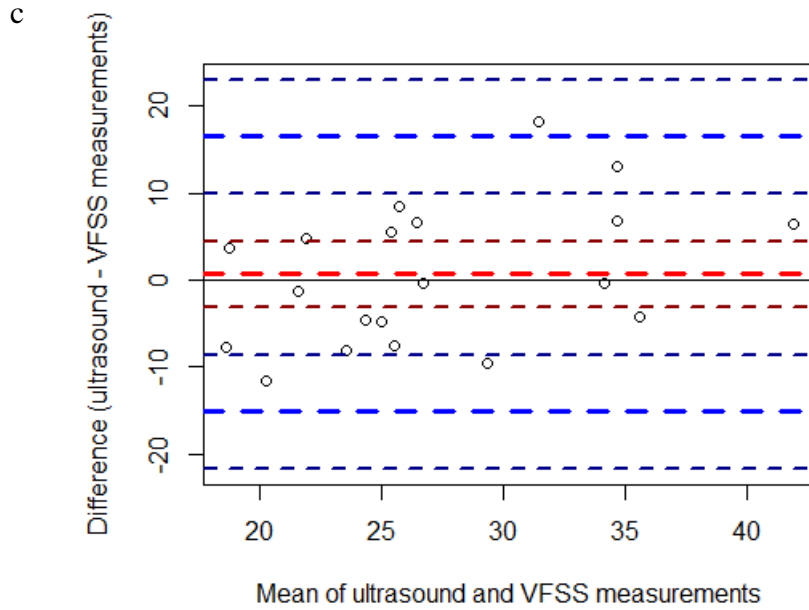
#### 7.2.2.2. Agreement

The same data were excluded from analysis as for correlation analyses. Assumptions for agreement analyses were met for hyoid excursion and thyrohyoid approximation. For hyoid excursion during dry, liquid, and puree swallowing, the upper limits of agreement for ultrasound measurements were calculated at 10.86 percentage change for dry swallows, 14.50 percentage change for liquid swallows, and 16.48 percentage change for puree swallows. The lower limits were calculated at -6.27 percentage change for dry swallows, -6.71 percentage change for liquid swallows, and -15.15 percentage change for puree swallows. This indicates that ultrasound measures of hyoid excursion during dry swallowing, for example, may be 10.86 percentage change above and 6.27 percentage change below videofluoroscopic measures. Upper limits of agreement for ultrasound measurements of thyrohyoid approximation were calculated at 44.67 percentage change for dry swallows, 35.67 percentage change for liquid swallows, and 42.92 percentage change for puree swallows. The lower limits were calculated

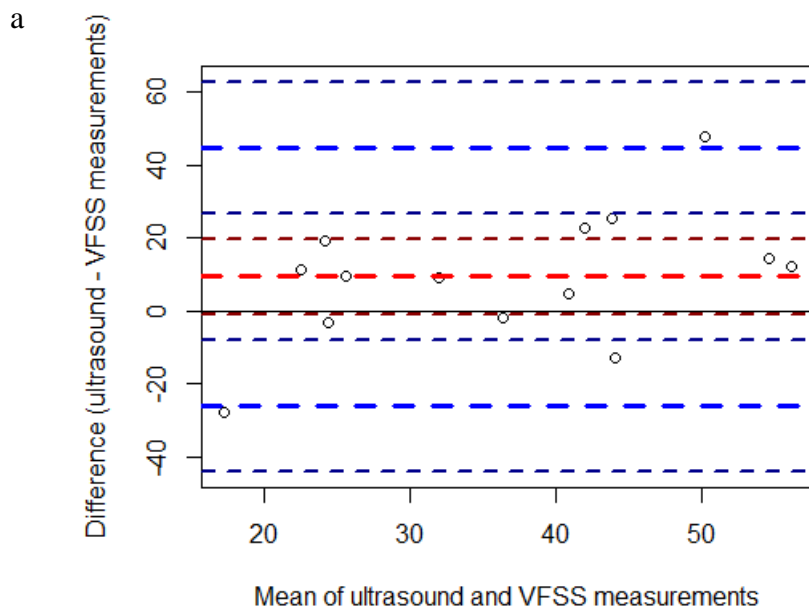
at -25.94 percentage change for dry swallows, -26.18 percentage change for liquid swallows, and -27.72 percentage change for puree swallows.

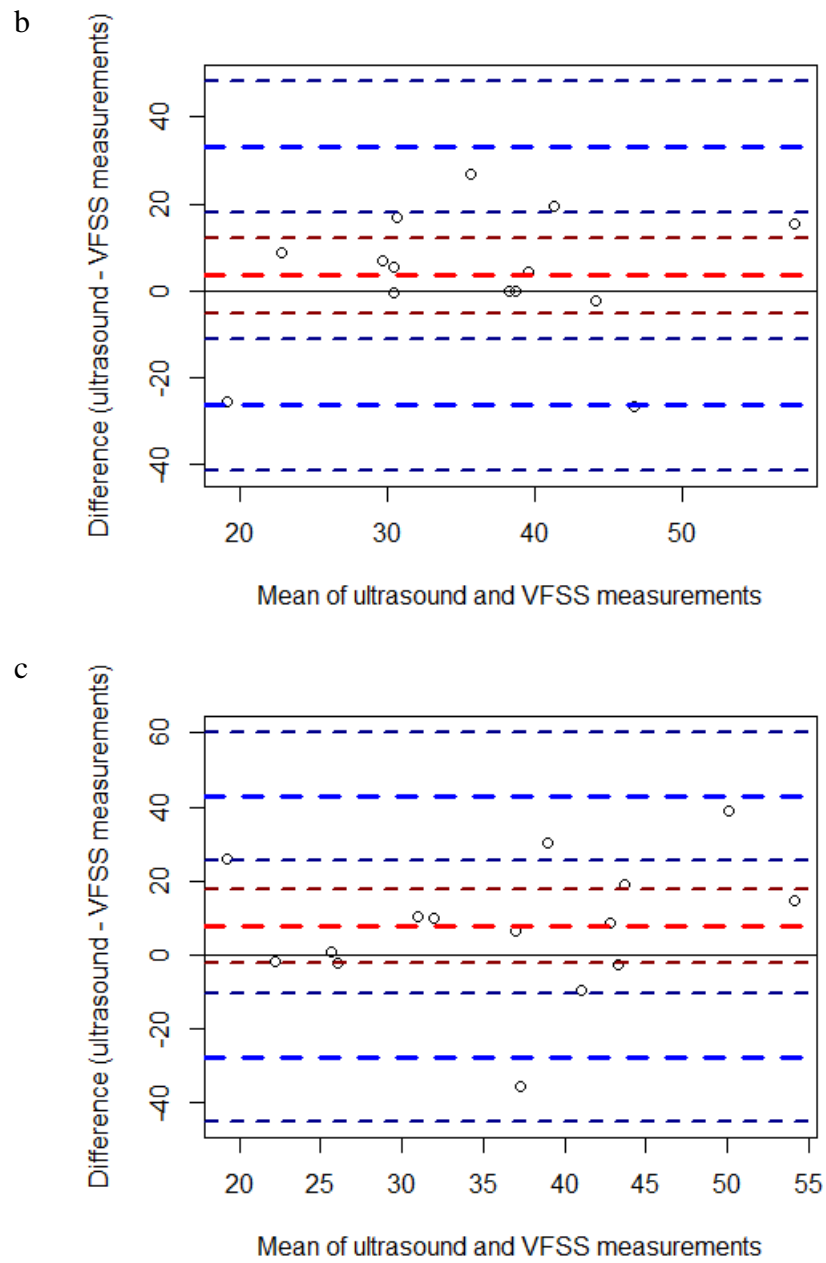
The Bland Altman plots indicate significant bias between ultrasound and videofluoroscopy for hyoid excursion during dry and liquid swallowing (Figure 17, a-b) since zero on the Y-axis did not lie within the 95% confidence interval of the mean difference. For hyoid excursion during puree swallowing (Figure 17, c) and for thyrohyoid approximation (Figure 18, a-c) during swallows of all consistencies, the zero on the Y-axis lay within the 95% confidence interval of the mean difference. This indicates a smaller bias between the two instrumentation.





**Figure 17.** Bland Altman plot for hyoid excursion during dry (a), liquid (b), and puree swallowing (c) assessed using ultrasound and videofluoroscopy (VFSS). The unit of the X- and Y-axis is percentage change. The thick dashed red line represents the mean difference between ultrasound and videofluoroscopic measurements; the thin dashed red lines represent the 95% confidence interval of the mean difference. There is bias of the two instruments if the black line of equality (theoretical mean difference of zero on the Y-axis) does not lie within the 95% confidence interval of the mean difference. The thick dashed blue lines represent the upper and lower limits of agreement; the thin dashed blue lines represent the 95% confidence intervals.





**Figure 18.** Bland Altman plot for thyrohyoid approximation during dry (a), liquid (b), and puree swallowing (c) assessed using ultrasound and videofluoroscopy (VFSS).

### **7.3. Study 2: Reliability Study**

#### **7.3.1. Material and Methods**

##### *7.3.1.1. Participants*

Reliability data were collected from the same 20 participants as those that participated in the Validity Study.

##### *7.3.1.2. Raters*

Five raters were involved in the Reliability Study in total. Three researchers (Rater 1, Rater 2, Rater 3) collected data for assessment of intra- and inter-rater reliability of data acquisition. The principal researcher (Rater 1) acquired data for evaluation of test-retest reliability. Rater 4 was involved in assessment of offline video measurement, and Rater 5 in evaluation of offline image measurement reliability. The number of raters involved in inter-rater reliability is consistent with previous research. The main analysis of acquisition inter-rater reliability involved three raters in total (Macrae et al., 2012) while the secondary analysis of measurement inter-rater reliability involved two raters (Hsiao et al., 2012; Huang et al., 2009). One of the five raters did have long-term experience in ultrasound imaging for swallowing assessment while the other raters were trained for purpose of this study.

##### *7.3.1.3. Instrumentation*

The Clarius™ ultrasound system, as described previously, was used. In addition to the curvilinear scanner (Figure 11), a linear scanner was utilised for assessment of the floor of mouth muscles (frequency range: 4 - 13 MHz, depth: 1 - 7 cm) (Figure 19).



**Figure 19.** Pocket-sized linear Clarius™ ultrasound scanner.

#### 7.3.1.4. *Study Preparation*

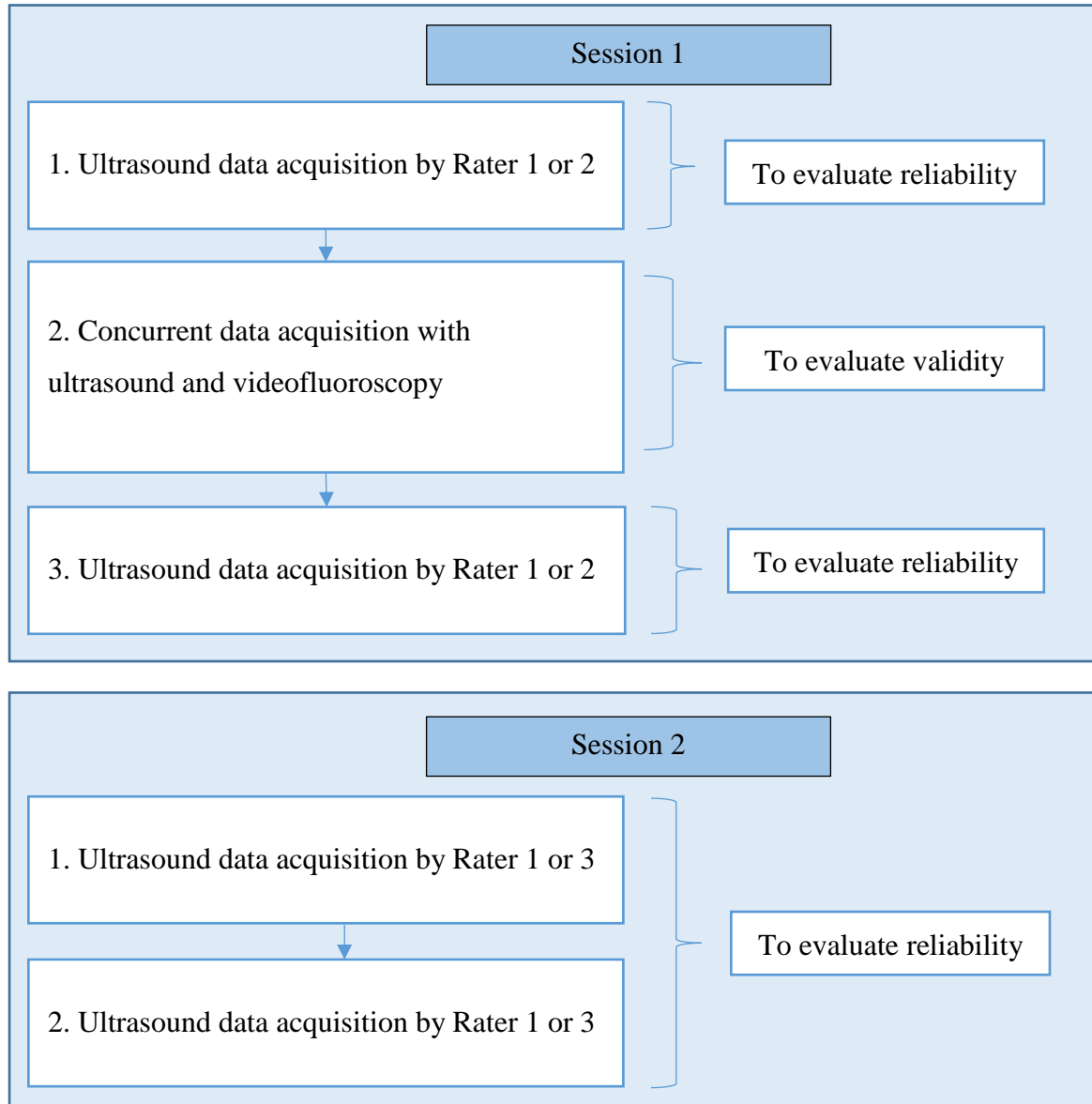
The study preparation was consistent with that stated for the Validity Study. Training was consensus-based rather than standardised as there is a lack of reported guidelines for standardised training protocols. Further, a main focus of this study was development and standardisation of measurement techniques while standardisation of training protocols will be an important next step. Measurement techniques for tongue thickness and CSA of the floor of mouth muscles were newly developed as described in section 7.3.1.6.

#### 7.3.1.5. *Procedure*

Reliability data were collected in two sessions. A period of at least 11 days between sessions was implemented to avoid learning or recall for the raters (Vaz, Falkmer, Passmore, Parsons, & Andreou, 2013). At the beginning of the first session, Rater 1 or 2 acquired ultrasound data for hyoid excursion, thyrohyoid approximation, tongue thickness, and CSA of the bilateral geniohyoid as a single unit and of the bilateral anterior belly of the digastric muscles. Following concurrent ultrasound and videofluoroscopic imaging for validation purposes, the second of the two raters collected the above-specified ultrasound measures. At the second session, ultrasound measures were acquired by Raters 1 and 3 (Figure 20). For each participant and session, randomisation was used to determine which of the two raters acquired data first. Raters were blinded to the measurements performed by other raters.

##### 7.3.1.5.1. *Setting*

Participants were asked to maintain a sitting position with the hips as far back in the chair as comfortably possible. They were instructed to keep their head in a neutral position, avoiding head flexion or extension. As stated for the Validity Study, no head immobilisation instrumentation or transducer stabilisation was applied to facilitate potential bedside application in the future and as there is not strong evidence to support the use of transducer stabilisation for increased accuracy of swallowing measures (Perry et al., 2016). The chair was placed in a way that the participants did not see the iPad screen, in order to avoid influence of biofeedback on performance.



**Figure 20.** Procedure: Flow-chart of data acquisition in session 1 and session 2.

#### 7.3.1.5.2. *Order and Number of Measures*

The order in which the different swallowing measures were collected within a session was determined by randomisation for each participant. It is recommended in the literature (Portney & Watkins, 2009) that data regarding intra-rater reliability should be collected for all raters involved in assessment of inter-rater reliability. To enable calculation of intra-rater reliability of Raters 1 - 3, each rater acquired each measure multiple times rather than once only. Rater 1 and 2 collected data for each measure twice per bolus consistency in succession. Rater 3 collected an additional data point per measure and bolus consistency for purpose of a co-occurring study. Individual scans were immediately repeated if the target structures were not clearly visible.

#### 7.3.1.5.3. *Bolus*

For data acquisition of hyoid excursion and thyrohyoid approximation, bolus swallowing was involved as described previously in the Validity Study (saliva, water, apple sauce). For assessment of tongue thickness, participants held a bolus on the tongue during scanning. A bolus hold position was used for measurements in an attempt to have the tongue in a relatively consistent position for measurements within and across participants. Further, a bolus on the tongue provided a landmark for measurement that is relatively easy to visualise. Boluses assessed for tongue thickness included 5 mL of each of the following on their tongue: apple sauce (brand Wattie's), vanilla custard (brand Wattie's), and olive oil. Bolus types with differing fat consistencies were used to explore whether bolus echogenicity impacted reliability (Rocha et al., 2015; M. Singh et al., 2010). Fat is considered a hyperechoic structure (Kristensen, 2011) while material rich in water is hypoechoic (Gosling, 1989).

#### 7.3.1.5.4. *Instruction*

For assessment of hyoid movement and thyrohyoid approximation, participants were instructed to swallow naturally once the scanner was placed. For assessment of tongue thickness, participants were asked to maintain a holding position of the bolus on their tongue during scanning. The instruction for assessment of the floor of mouth muscles was to relax and to keep the mouth closed without swallowing or holding a bolus. Methods for measurement of bolus quantities and bolus administration were performed as described for the Validity Study. To mimic the sequence commonly followed in clinical practice, the order in which different bolus types were presented was kept consistent across participants and sessions for hyoid excursion and thyroid approximation (saliva, water, apple sauce) as well as for tongue thickness (apple sauce, vanilla custard, olive oil).

#### 7.3.1.5.5. *Recording*

Recordings of hyoid excursion and thyrohyoid approximation were performed as previously stated. Table 8 provides information about the recordings specific to the remaining measures. Notably, transducer positioning was not controlled across trials and session to allow for increased clinical applicability. All acquired ultrasound videos and images displaying measurement cursors were saved and uploaded to the Clarius™ Cloud. For purpose of evaluation of offline image measurement reliability, some of the measured images were additionally saved without the measurement cursors. Randomisation was used to determine one image per measure and bolus consistency for each participant to be used for performance



of offline measurements; only data collected by Rater 1 at the first or second session were included.

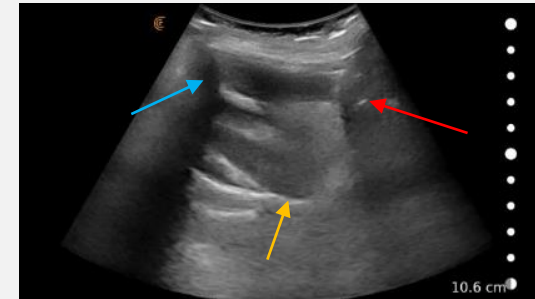
#### 7.3.1.6. *Data Extraction*

*Acquisition reliability:* For assessment of acquisition reliability, data extraction was performed online on the iPad after each swallow. First, specific images of the recorded videos were selected for measurement. Then, measurements were performed online using a straight-line or a free-hand tool; these tools were guided by hand or by use of a touch pen. Measurements were written on a Word document before they were transferred to an Excel file by the main rater after the session. To minimise errors, a second person checked the transferred numbers visually.

*Offline measurement reliability:* For evaluation of offline measurement reliability, previously acquired data that were stored in the Clarius™ Cloud were re-measured offline. Raters involved in assessment of measurement intra- and inter-rater reliability derived measurements on two occasions, a minimum of 11 days apart, to avoid recall (Vaz et al., 2013). For offline videos measurement reliability, videos were downloaded from the Clarius™ Cloud. Videos were then reviewed using QuickTime Player (QuickTime Player Version 7.7.9) for image selection. Finally, measurements of the selected images were performed using ImageJ, public domain software developed by the National Institute of Health (Schneider, Rasband, & Eliceiri, 2012).

**Table 8.** Ultrasound recording: Measurement specific information

Measure	Scanner; Name of pre-setting	Imaging method
Tongue thickness	Curvilinear; Clarius™ ‘Abdomen’ pre-setting (depth: 7-10 cm, frequency: 4 MHz, single focus, dynamic range: 52 dB)	A sagittal sonogram was performed with the scanner positioned at right angles to the floor of mouth muscles (FOM) (E. H. Oh et al., 2016). The scanner was placed midline, capturing the acoustic shadow of the mandible on one side (blue arrow) and on the other side the acoustic shadow of the hyoid (red arrow). Inferiorly, the surface of the tongue (yellow arrow) was visible. A sagittal rather than a coronal imaging method was selected as there is a lack of objective criteria for anterior-posterior transducer placement for coronal imaging (Nakamori et al., 2016; Tamura, Kikutani, Tohara, Yoshida, & Yaegaki, 2012).
CSA of the FOM	Linear; Clarius™ ‘Breast’ pre-setting (depth: 3 - 5 cm, frequency: 10 MHz, dual focus, dynamic range: 65 dB)	A coronal sonogram was obtained with the scanner placed at a right angle to the FOM. The muscles were scanned from mandible towards hyoid (Watkin et al., 2001) to find the largest boundaries for each muscle. The clearest muscle boundaries were used as a second criteria to allow for accurate measurements. The scanner was held, as much as possible, with minimal and even pressure on the LAB and RAB to minimise size differences resulting from examiner error. <sup>13</sup>



Note. FOM = floor of mouth muscles, CSA = cross-sectional area, GH = geniohyoid muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

<sup>13</sup> To determine the anterior-posterior transducer location to measure the CSA of the floor of mouth muscles, Watkin and colleagues (2001) reported a method to calculate the midframe between mandible and hyoid. However, this method was not feasible for online data extraction in this study. Further, previous research reported to place the transducer at approximately halfway between mandible and hyoid (Perry et al., 2016) or mandible and thyroid cartilage (Macrae, Jones, Myall, Melzer, & Huckabee, 2013). As midway placement may be prone to subjectivity, the present study used more detailed criteria for transducer placement. However, it is acknowledged that different muscle sections may have been measured within and across participants. Ongoing investigation of CSA measurement, such as comparison of different methods, is indicated.

For offline image measurement reliability, images previously selected online during acquisition were downloaded and raters performed the measurements on these pre-selected images using ImageJ. Calibration of each image was required prior to offline measurement. A digital drawing pad (Wacom Intuos Pen Tablet) was utilised for measurement of the floor of mouth muscles to allow for precise guidance of the free-hand tool.

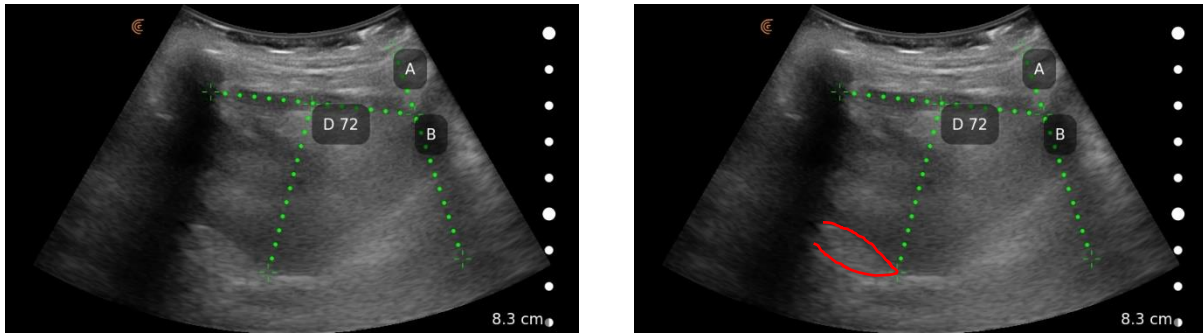
#### *7.3.1.6.1. Hyoid Excursion and Thyrohyoid Approximation*

Image selection and measurement techniques for hyoid excursion and thyrohyoid approximation were performed as described for the ultrasound measurements in the Validity Study.

#### *7.3.1.6.2. Tongue Thickness*

*Image selection:* For data extraction of tongue thickness, a single image was selected showing the bolus on the tongue as clearly as possible during the participant's bolus hold position. The bolus generally appeared as a triangle between the tongue surface and palate as depicted in Figure 21.

*Measurement:* For measurement, three single straight lines were utilised. First, the best fit line (Line A) was drawn along the anterior border of the shadow of the hyoid. For Line B, one calliper was placed at the posterior aspect of the onset of the black shadow created by the mental spine. The other calliper was placed where Line A intersects the onset of the shadow of the hyoid. For Line D, one calliper was placed at midpoint on Line B, the other calliper was placed at the posterior edge of the bolus ('point of the triangle'). The tongue thickness was extracted in mm. This measurement technique was newly developed as prior research did not report reliable (J.-W. Chen, Chang, Wang, Chang, & Huang, 2014) or replicable measurements (E. H. Oh et al., 2016).

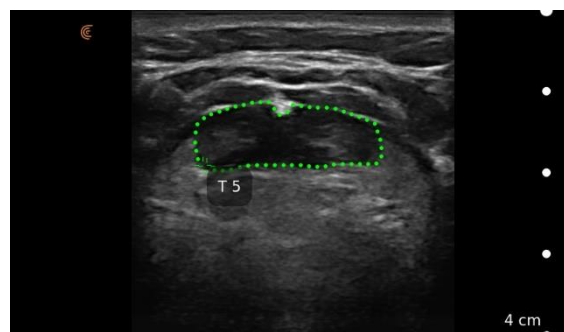


**Figure 21.** Sonogram of the tongue thickness (D 72). The left and right images are identical, with exception of the bolus outlined in red on the right image. Part of the bolus is obscured by the shadow cast by the mandible.

#### 7.3.1.6.3. *CSA of the Geniohyoid Muscles*

*Image selection:* Data extraction of the CSA of the geniohyoid muscles involved selection of the image showing the largest and clearest muscle boundary.

*Measurement:* The freehand measurement tool was used to trace around the outside of the muscle (Figure 22). The mylohyoid muscles were included at the superior border of the geniohyoid muscles as a visual distinction between the two muscles was often not possible<sup>14</sup>. The CSA was extracted in mm<sup>2</sup>.



**Figure 22.** Sonogram of the cross-sectional area (CSA) of the geniohyoid<sup>+</sup> muscles.

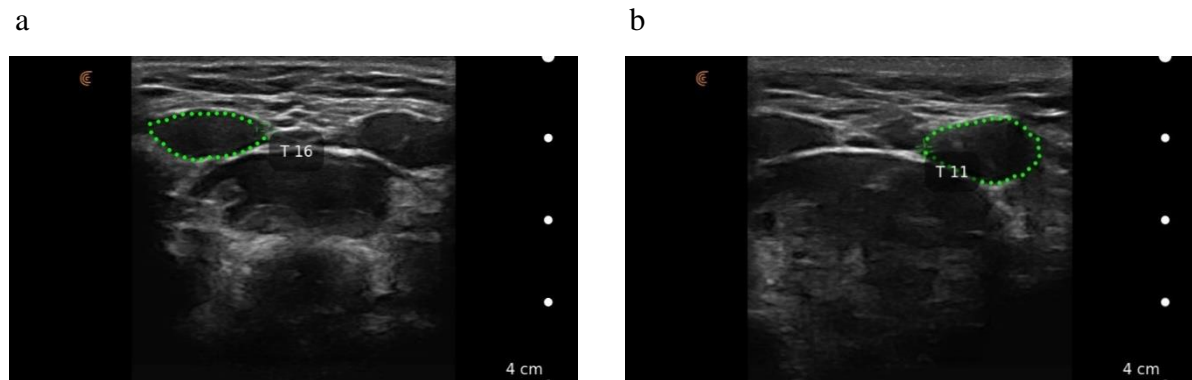
#### 7.3.1.6.4. *CSA of the Left and Right Anterior Belly of the Digastric Muscles*

*Image selection:* To extract data of the CSA of the left and right anterior belly of the digastric muscles, the image showing the largest and clearest muscle boundary was selected.

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<sup>14</sup> For this reason, this measurement will be referred to as geniohyoid<sup>+</sup> muscles.

*Measurement:* With the freehand measurement tool, a trace around the outside of each muscle (excluding connective tissue) was drawn (Figure 23). The CSA was extracted in mm<sup>2</sup>.



**Figure 23.** Sonogram of the cross-sectional area (CSA) of the left (a) and right (b) anterior belly of the digastric muscles.

#### 7.3.1.7. Data Analysis

Means and standard deviations were calculated for each measure across participants; these statistics were based on the first swallow acquired by Rater 1 at the first session.

##### 7.3.1.7.1. Types of Reliability

Figure 24 illustrates the reliability types that were assessed in this study, included are components considered for data analysis.

SCANNING	IMAGE SELECTION	MEASUREMENT
Acquisition Reliability (Intra-, inter-rater reliability, test-retest reliability)		
Offline Measurement Reliability (Video) (Intra-, inter-rater reliability)		
		Offline Measurement Reliability (Image) (Intra-, inter-rater reliability)

**Figure 24.** Three reliability types across the components of data analysis: Acquisition reliability, offline measurement reliability (video), and offline measurement reliability (image).

#### 7.3.1.7.2. *Measures of Reliability*

Reliability was quantified using different measures. The ICC was calculated for intra-, inter-rater, and test-retest reliability as a relative measure of reliability to allow for comparison of study findings to results of other studies. Further, the SEM was assessed as an absolute measure of reliability to quantify measurement errors in the unit of individual measures. Confidence intervals were reported for the ICC and the SEM to provide information about precision of these estimates (Bartlett & Frost, 2008; Koo & Li, 2016; Stratford & Goldsmith, 1997). Since the ICC depends on both the extent of measurement error and the homogeneity of the sample (Bartlett & Frost, 2008), the between-subject variance was reported as a measure of the sample homogeneity. For acquisition reliability, evaluation of a systematic rater effect was performed for inter-rater reliability to understand whether any single rater acquired systematically different measures compared to the other raters. A systematic session effect was assessed for test-retest reliability to detect whether systematic error arose from factors such as learning or fatigue in repeated testing (Weir, 2005).

#### 7.3.1.7.3. *Analysis Procedure*

First, data were plotted using scatter plots. Linear mixed effects analyses were performed using R software (R Core Team, 2016) and lme4 (Bates et al., 2015). Model selection and ICC calculation for acquisition and measurement reliability are detailed in Table 9 and Table 10, respectively. Differences in analyses methods between acquisition and measurement reliability are discussed further below. A bootstrap distribution was calculated from which the 95% confidence interval for each ICC was obtained. Residual versus fitted plots were used to ensure homoscedasticity patterns; Q-Q plots of the residuals were visually inspected to identify potential deviation from normality. For reporting, the guidelines published by Kottner and colleagues (2011) were considered. For interpretation of the results, criteria reported by Portney and Watkins (2009) were used: poor reliability ( $ICC < 0.50$ ), moderate reliability ( $ICC 0.50 - 0.75$ ), and good reliability ( $ICC > 0.75$ ).

As depicted in Table 9 and Table 10, different models and ICC calculations were selected for acquisition and measurement reliability. A two-way random model was used for both acquisition intra- and inter-rater reliability, as suggested by Bartlett and Frost (2008). This model was selected because each participant was rated by the same raters (fully crossed design); subjects and raters were entered as random effects because the subjects involved represented a random sample of the population of healthy adults or raters, respectively (Bartlett

& Frost, 2008; Hallgren, 2012). For test-retest acquisition reliability, a two-way mixed effects model was used as all subjects were rated by the same rater and as repeated measures cannot be treated as random (Weir, 2005). Since all raters involved in data acquisition performed more than one measurement per measure and participant, information of intra-rater reliability was available for each rater. Hence, a method for calculation of inter-rater ICCs was selected that includes information about intra-rater-reliability, as suggested by Bartlett and Frost (2008). Accordingly, for calculation of intra-rater ICCs, data about inter-rater reliability was included. Differently, for measurement intra-rater reliability, a two-way mixed model was utilised as different measurements performed by the same rater are related. For measurement inter-rater reliability, a two-way random effects model was selected as both raters assessed each participant. Different ICC calculation methods were selected for measurement reliability compared to acquisition reliability since each rater obtained only one measurement per measure and participant (Koo & Li, 2016).

For both acquisition and measurement reliability, the effect of bolus on reliability was tested for hyoid excursion and thyrohyoid approximation. Using a likelihood ratio test, the full model which included bolus as a fixed effect was compared the reduced model that did not contain bolus as a fixed effect. If there was a significant bolus effect, analysis using the full model was continued. If there was no bolus effect, the reduced model was used. Since the effect of bolus was considered in the model selection, one ICC was calculated across bolus types. This method was used for hyoid excursion and thyrohyoid approximation since visibility of the bolus is not required for measurement. For tongue thickness, bolus visibility is required for measurement. Thus, one ICC per bolus type was calculated.

The SEM was calculated as the square root of the residual variance of the random effects. The between-subject standard deviation was calculated as the square root of the participant variance of the random effects. For acquisition reliability, presence of a potential systematic error was tested by comparing two models using a likelihood ratio test. The full model contained the factor in question as a fixed factor, namely 'rater' for assessment of a systematic rater effect (inter-rater reliability) and 'session' for evaluation of a systematic rater effect (test-retest reliability). If an effect of the fixed factor was identified, the error was quantified based on the coefficient estimates of the fixed effects. An error with a  $p$ -value  $\leq .05$  was considered significant.

**Table 9.** Analysis methods for acquisition reliability

Reliability	Data included into analysis	Model selection	Formula for ICC calculation
Acquisition intra-rater reliability	One ICC was calculated based on all measures acquired by Rater 1 and Rater 2 at Session 1, and by Rater 3 at Session 2. For Rater 1, data of Session 2 were excluded to avoid potential influence of learning from Session 1 to Session 2.	<i>ICC(2,1)</i> : 2-way random effects model based on single measures: subject and rater were entered as random effects. For fixed effects an intercept only was entered. The effect of bolus was tested for some measures as stated previously.	$\frac{\text{between subject variance} + \text{between rater variance}}{\text{between subject variance} + \text{between rater variance} + \text{residual variance}}$
Acquisition inter-rater reliability	One ICC was calculated based on the same measures as for evaluation of acquisition intra-rater reliability.	<i>ICC(2,1)</i> : 2-way random effects model based on single measures: subject and rater were entered as random effects. For fixed effects an intercept only was entered. The effect of bolus was tested for some measures as stated previously.	$\frac{\text{between subject variance}}{\text{between subject variance} + \text{between rater variance} + \text{residual variance}}$
Acquisition test-retest reliability	One ICC was calculated using all measures collected by Rater 1 in both sessions.	<i>ICC(3,1)</i> : 2-way mixed effects model based on single measures: subject was entered as random effects, session as fixed effects. The effect of bolus was tested for some measures as stated previously.	$\frac{\text{between subject variance}}{\text{between subject variance} + \text{residual variance}}$

Note. ICC = intraclass correlation coefficient



**Table 10.** Analysis methods for measurement reliability

Reliability	Data included into analysis	Model selection	Formula for ICC calculation
Offline measurement intra-rater reliability	For image measurement reliability, separate ICCs were calculated for Rater 1 and for Rater 4. For video measurement reliability, separate ICCs were calculated for Rater 1 and Rater 5.	<i>ICC(3,1)</i> : 2-way mixed effects model based on single measures: subject was entered as random effects, measurement trial as fixed effects. The effect of bolus was tested for some measures as stated previously.	$\frac{\text{between subject variance}}{\text{between subject variance} + \text{residual variance}}$
Offline measurement inter-rater reliability	For image measurement reliability, one ICC was calculated for Rater 1 and Rater 4. For video measurement reliability one ICC was calculated for Rater 1 and Rater 5. For analysis, the first measurement attempt of each rater was considered.	<i>ICC(2,1)</i> : 2-way random effects model based on single measures: subject and rater were entered as random effects. For fixed effects an intercept only was entered. The effect of bolus was tested for some measures as stated previously.	$\frac{\text{between subject variance}}{\text{between subject variance} + \text{between rater variance} + \text{residual variance}}$

*Note.* ICC = intraclass correlation coefficient

### 7.3.2. Results

As stated for the Validity Study, 20 females and 10 males were recruited with five participants in each targeted age group. The two sessions were completed by all participants. For one participant, one online measurement of thyrohyoid approximation was missing; thus, it could not be included in analysis of acquisition reliability. For video measurement reliability, one measurement of hyoid excursion and one of tongue thickness were missing for one subject, and one measurement of hyoid excursion was missing for a second subject due to data saving issues. For image measurement reliability, two measurements of thyrohyoid approximation could not be derived for one subject due to failed upload of data to the Clarius™ Cloud. Table 11 below reports means and standard deviations for all measures and bolus consistencies using ultrasound.

**Table 11.** Ultrasound measures: Mean and standard deviation

Measure	Bolus	Mean (SD)
Hyoid excursion	Dry	24.06 percentage change (8.90)
	Liquid	28.29 percentage change (5.11)
	Puree	26.86 percentage change (7.66)
	Dry, liquid, puree	26.40 percentage change (7.48)
Thyrohyoid approximation	Dry	40.45 percentage change (15.80)
	Liquid	42.80 percentage change (13.20)
	Puree	39.57 percentage change (17.09)
	Dry, liquid, puree	40.94 percentage change (15.25)
Tongue thickness	Apple sauce	52.09 mm (5.74)
	Vanilla custard	52.03 mm (6.14)
	Olive oil	50.09 mm (6.92)
FOM	GH <sup>+</sup>	215.16 mm <sup>2</sup> (65.86)
	LAB	73.95 mm <sup>2</sup> (28.23)
	RAB	72.15 mm <sup>2</sup> (23.67)

*Note.* SD = standard deviation, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

#### 7.3.2.1. Acquisition Reliability

Results of intra-, inter-rater, and are shown in Table 12, findings for test-retest reliability are depicted in Table 13. There was an effect of bolus for intra-, inter-rater reliability ( $p < .001$ ),

and test-retest reliability ( $p < .001$ ) of hyoid excursion; thus, bolus was entered as a fixed effect into the model. No bolus effect was found for intra-, inter-rater, and test-retest reliability of thyrohyoid approximation. There was evidence for poor intra-, inter-rater, and test-retest reliability of hyoid excursion and thyrohyoid approximation.

**Table 12.** Intra- and inter-rater reliability for ultrasound data acquisition

Measure	Bolus	Intra-rater ICC (95% CI)	Inter-rater ICC (95% CI)	SEM (95% CI)	Between-subject SD
Hyoid excursion	Dry, liquid, puree	.38 (.22, .52)	.34* (.18, .49)	5.87 percentage change (5.47, 6.28)	4.38 percentage change
Thyrohyoid approximation	Dry, liquid, puree	.38 (.21, .53)	.32* (.16, .47)	11.90 percentage change (11.12, 12.78)	8.62 percentage change
Tongue thickness	Apple sauce	.56 (.33, .71)	.56 (.32, .71)	3.70 mm (3.28, 4.23)	4.16 mm
	Vanilla custard	.70 (.51, .82)	.68* (.47, .81)	3.33 mm (2.94, 3.80)	5.04 mm
	Olive oil	.70 (.50, .82)	.70 (.51, .82)	3.82 mm (3.38, 4.36)	5.88 mm
FOM	GH <sup>+</sup>	-. [.71 (.50, .84)	-.49* (.25, .71)	35.59 mm <sup>2</sup> (31.49, 40.66)	46.08 mm <sup>2</sup>
	LAB	-. [.68 (.49, .80)	-.63* (.41, .77)	14.61 mm <sup>2</sup> (12.93, 16.70)	20.54 mm <sup>2</sup>
	RAB	-. [.67 (.48, .79)	-.61* (.39, .75)	12.78 mm <sup>2</sup> (11.31, 14.60)	17.38 mm <sup>2</sup>

*Note.* ICC = intraclass correlation coefficient, CI = confidence interval, SEM = standard error of measurement, SD = standard deviation, \*significant rater effect at  $p \leq .05$ , FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles; RAB = right anterior belly of the digastric muscles, [] = assumptions for analysis are not met

For tongue thickness, the data revealed moderate intra- and inter-rater reliability and good test-retest reliability. Comparison of reliability of tongue thickness between different bolus types showed higher intra-, inter-rater, and test-retest reliability for vanilla custard and olive oil than for apple sauce. Intra- and inter-rater reliability of CSA of the floor of mouth muscles could not be evaluated as the assumptions for analysis were not satisfied. While test-retest reliability was moderate for geniohyoid<sup>+</sup> muscles and left anterior belly of the digastric muscles, it was

good for right anterior belly of the digastric muscle. Notably, large confidence intervals for most of the ICCs across the analysed measures indicate considerable uncertainty regarding the reliability estimates.

**Table 13.** Test-retest reliability for ultrasound data acquisition

Measure	Bolus	ICC (95% CI)	SEM (95% CI)	Between- subject SD
Hyoid excursion	Dry, liquid, puree	.45* (.25, .61)	4.74 percentage change (4.29, 5.18)	4.30 percentage change
Thyrohyoid approximation	Dry, liquid, puree	.43 (.22, .57)	10.58 percentage change (9.64, 11.63)	9.11 percentage change
Tongue thickness	Apple sauce	.65 (.40, .80)	3.19 mm (2.67, 3.83)	4.36 mm]
	Vanilla custard	.76 (.56, .87)	2.90 mm (2.43, 3.48)	5.10 mm
	Olive oil	.76 (.57, .87)	3.31 mm (2.77, 3.97)	5.86 mm
	GH <sup>+</sup> -	.66 (.43, .80)	36.87 mm <sup>2</sup> (30.88, 44.23)	51.18 mm <sup>2</sup>
FOM	LAB -	.62* (.36, .79)	16.20 mm <sup>2</sup> (13.57, 19.43)	20.55 mm <sup>2</sup>
	RAB -	.79* (.61, .88)	11.29 mm <sup>2</sup> (9.46, 13.54)	22.05 mm <sup>2</sup>

*Note.* ICC = intraclass correlation coefficient, CI = confidence interval, SEM = standard error of measurement, SD = standard deviation, \*significant rater effect at  $p \leq .05$ , [] =assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscle

A rater effect for inter-rater reliability was found for acquisition of the majority of the analysed measures; detailed information is included in the *Appendix B.3*. There was a session effect for test-retest reliability for acquisition of hyoid excursion and CSA of the left and right anterior belly of the digastric muscles. Detailed information is illustrated in *Appendix B.4*.

#### 7.3.2.2. Offline Measurement Reliability (Video)

For intra-rater reliability of Raters 1 and 4, there was a bolus effect for hyoid excursion ( $p = .001$ ,  $p < .001$ , respectively); thus, bolus was included as a fixed effect into the model. No bolus effect was found for thyrohyoid approximation. For inter-rater reliability, a bolus effect was found for hyoid excursion ( $p < .001$ ), there was no bolus effect for thyrohyoid approximation.

Poor to moderate intra-rater, and poor inter-rater reliability was found for hyoid excursion. Reliability was consistently poor for thyrohyoid approximation. For tongue thickness and CSA of the floor of mouth muscles, there was evidence for moderate to good intra-rater reliability; inter-rater reliability was moderate. ICCs for intra- and inter-rater video measurement reliability are reported in Table 14. SEMs and between-subject standard deviations are shown in *Appendix B.5*.

**Table 14.** Intra- and inter-rater reliability for offline measurement (video) of Rater 1 and Rater 4

Measure	Bolus	Intra-rater ICC (95% CI)	Intra-rater ICC (95% CI)	Inter-rater ICC (95% CI)
Hyoid excursion	Dry, liquid, puree	.45 (.22, .65)	.53 (.30, .71)	.44 (.22, .60)
Thyrohyoid approximation	Dry, liquid, puree	.41 (.20, .60)	.31 (.09, .50)	.28 (.09, .49)
Tongue thickness	Apple sauce	.75 (.47, .90)	.79 (.57, .92)	.62 (.24, .87)
	Vanilla custard	.90 (.78, .96)	[.72] (.44, .88)	.56 (.24, .86)
	Olive oil	.83 (.62, .94)	.88 (.74, .95)	.60 (.24, .90)
GH <sup>+</sup>	-	[.72] (.46, .88)	.85 (.74, .95)	.64 (.29, .88)
FOM LAB	-	.96 (.90, .98)	[.76] (.52, .90)	[.45] (.12, .73)
RAB	-	.87 (.69, .95)	.64 (.32, .84)	[.34] (<.001, 0.69)

*Note.* ICC = intraclass correlation coefficient, CI = confidence interval, [] = assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

### 7.3.2.3. Offline Measurement Reliability (Image)

For intra-rater reliability of hyoid excursion an effect of bolus was found for Rater 1 ( $p < .001$ ) and for Rater 5 ( $p < .001$ ); hence, bolus was included as a fixed effect into the model. For intra-rater reliability of thyrohyoid approximation, there was no effect of bolus for Rater 1 but for Rater 5 ( $p = .01$ ). For inter-rater reliability, a bolus effect was found for hyoid excursion ( $p < .001$ ) but not for thyrohyoid approximation.

The results indicate poor to moderate intra-rater reliability of hyoid excursion; inter-rater reliability was moderate. Poor reliability was revealed for thyrohyoid approximation measure. For tongue thickness and for the CSA of the geniohyoid<sup>+</sup> muscles reliability was good. Good intra-rater and moderate inter-rater reliability were found for the CSA of the anterior bellies of the digastric muscles. ICCs for intra- and inter-rater image measurement reliability are depicted in Table 15. SEMs and between-subject standard deviations are shown in *Appendix B.6*.

**Table 15.** Intra- and inter-rater reliability for offline measurement (image) of Rater 1 and Rater 5

Measure	Bolus	Intra-rater ICC (95% CI)	Intra-rater ICC (95% CI)	Inter-rater ICC (95% CI)
Hyoid excursion	Dry, liquid, puree	.64 (.43, .79)	.49 (.23, .66)	.50* (.26, .67)
Thyrohyoid approximation	Dry, liquid, puree	.23 (.04, .42)	.49 (.28, .66)	.10 (.00, .27)
Tongue thickness	Apple sauce	[.91] (.79, .96)	[.83] (.64, .93)	[.68] (.36, .84)
	Vanilla custard	.80 (.60, .92)	.89 (.74, .96)	.77 (.53, .90)
	Olive oil	.94 (.86, .98)	[.86] (.67, .94)	[.84] (.64, .93)
GH <sup>+</sup>	-	.97 (.94, .99)	.96 (.91, .99)	.88 (.72, .95)
FOM	LAB	[.80] (.60, .92)	.96 (.91, .99)	[.94*] (.82, .98)
	RAB	.88 (.75, .96)	.95 (.88, .98)	.68* (.38, .87)

*Note.* ICC = intraclass correlation coefficient, CI = confidence interval, \*significant rater effect at  $p \leq .05$ , [] = assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

#### 7.4. Discussion

UES opening and hyolaryngeal excursion are commonly assessed using videofluoroscopy; yet, use of this instrumentation has limitations including issues with radiation safety (Enyinna, 2016) and clinical availability (Rugiu, 2007). There are some data suggesting that ultrasound is valid and reliable in the assessment of hyolaryngeal excursion using large ultrasound equipment (Y.-C. Chen et al., 2017; Hsiao et al., 2012; Huang et al., 2009). Commonly used diagnostic ultrasound devices are expensive and not easily portable, therefore pocket-sized

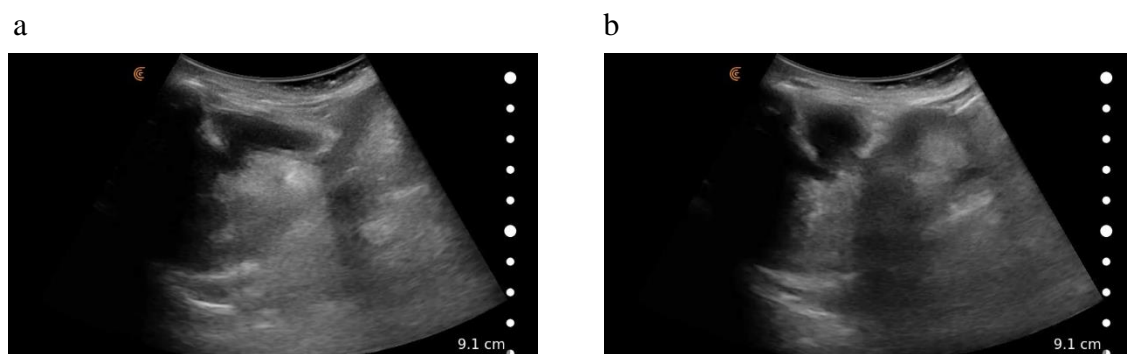
instrumentation may increase the potential for clinical translation. In contrast to previous reports of good validity and reliability of sophisticated ultrasound instrumentation, findings of this research indicate insufficient validity and reliability of the pocket-sized Clarius™ device for assessment of swallowing measures in healthy subjects.

#### **7.4.1. Validity Study**

Results of this study suggest that ultrasound measurements of hyoid excursion and thyrohyoid approximation assessed using the Clarius™ system in healthy subjects poorly reflect measurements derived from videofluoroscopy, with the exception of hyoid excursion during saliva swallowing. Yet, caution is warranted in the interpretation of the strong linear association between ultrasound and videofluoroscopic measurements of hyoid excursion for dry swallows as reliability was poor for this measure. Additionally, while intra-rater reliability for videofluoroscopic measurements was good, inter-rater reliability may have been insufficient. This contrasts with published data indicating good inter-rater reliability for maximum hyoid displacement and hyolaryngeal approximation for videofluoroscopy (R. Leonard, K. A. Kendall, & S. McKenzie, 2004b; Leonard, Kendall, & McKenzie, 2014; Martin-Harris et al., 2008). Thus, limitations in reliability of both methods of imaging may compromise validity. Values of hyoid excursion and thyrohyoid approximation obtained from ultrasound and videofluoroscopy were considerably different. This may be explained, in parts, by differences in measurement methods across instrumentation. As validity of instrumentation is of utmost importance, more research is needed to evaluate validity of pocket-sized ultrasound devices prior to transfer of such instrumentation in clinical swallowing assessment.

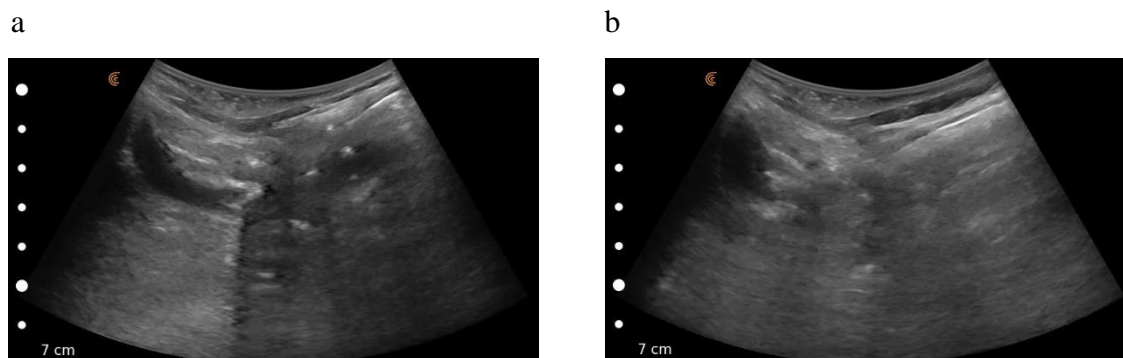
While there are data to suggest that larger, more sophisticated ultrasound instrumentation is valid in the assessment of hyolaryngeal excursion when compared to videofluoroscopy (Y.-C. Chen et al., 2017; Hsiao et al., 2012; Huang et al., 2009), this is the first study to validate swallowing measures using pocket-sized ultrasound equipment. Yet, pocket-sized ultrasound devices have been validated in other medical fields, such as gynaecology. In a study by Galjaard and colleagues (2014), agreement between various quantitative gynaecological measures derived from a pocket-sized and a sophisticated ultrasound system ranged from poor (ICC = 0.38) to good (ICC = 0.93) if considering the interpretation criteria by Portney and Watkins (2009). Notably, a different researcher operated the pocket-sized and large ultrasound system, thus the role of examiner cannot be ruled out.

Validity of any measure requires that the measures are acquired consistently (Field, Miles, & Field, 2012; Portney & Watkins, 2009). Thus, given our findings of insufficient reliability, an absence of clinical validity is not surprising. Poor reliability and validity as compared to published data may suggest that the Clarius™ system cannot match the image quality of larger, likely more expensive systems; good image quality is critical for clear tissue interfaces that allow for reliable measurements (Y. Ishida, Carroll, Pollock, Graves, & Leggett, 1992; Stone, 2005). Notably, the images presented in the sections 7.2.1.5.1 and 7.2.1.5.2 were selected due to clear image quality for optimal illustration of the measurement techniques. However, more representative images are shown in Figure 25 and Figure 26. Compromised image quality may arise from imaging settings, including focal point, frequency, and resolution (Stone, 2005). The pre-settings provided by Clarius™ may be appropriate for the measurements they were designed for (e.g. abdomen); however, further adaptation to swallowing measures may be required for optimised use of this technology. Unfortunately, a thorough comparison of technical aspects between small and large instrumentation is not possible, as technical details are not available for other published studies. This highlights the need for detailed documentation of methodology to allow for replication and data comparison across studies. Further, potential impact of participant variables such as neck anatomy on imaging quality (Stone, 2005) may have been pronounced for the pocket-sized system if image quality was decreased. Having used an ultrasound system that is in early development, substantial technical issues were encountered in this study. Unstable connection between the Clarius™ scanners and the iPad resulted in frequent interruption of data collection. Other technical issues, such as a malfunctioning scrolling function for video review likely impacted the study findings.



**Figure 25.** Sonogram depicting the hyoid at rest position (a) and at maximal displacement (b).





**Figure 26.** Sonogram depicting the hyoid and the thyrohyoid cartilage at rest (a) and at maximal approximation (b).

Apart from technical aspects, there are other factors that may partially explain differences between this study and published validity data. Our study was the first to assess concurrent validity; previous studies performed ultrasound and videofluoroscopic imaging separately (Y.-C. Chen et al., 2017; Hsiao et al., 2012; Huang et al., 2009). Concurrent ultrasound and videofluoroscopic data extraction yields the benefit that data derived from both modalities reflect the same event (Portney & Watkins, 2009). However, concurrent data acquisition posed a technical challenge that may have negatively affected validity. Stable transducer placement, known to be critical for quality of the recordings (Stone, 2005), may have been compromised as the researcher kept an arm-length distance from the participant for reason of radiation safety (Peladeau-Pigeon & Steele, 2013). For future studies, advantages and disadvantages of the use of a transducer stabilisation unit will need to be balanced with the advantage of concurrent data collection.

#### **7.4.2. Reliability Study**

Reliable data acquisition within and across raters, as well as over time, is a requirement for clinical application of pocket-sized ultrasound systems in swallowing assessment. The findings suggest that acquisition of swallowing measures using the Clarius™ system is insufficiently reliable. This is indicated by low ICCs and large SEMs for intra- and inter-rater reliability and for test-retest reliability in relation to the mean hyoid excursion and thyrohyoid approximation.

Results of this study contrast with reliability findings of published studies using larger ultrasound equipment. Good intra- and inter-rater acquisition reliability ( $ICC > 0.75$ ) has been reported for hyoid excursion (Hsiao et al., 2012), thyrohyoid approximation (Huang et al., 2009), and for sagittal CSA of the geniohyoid muscles (Shimizu et al., 2016) in healthy subjects. Further, there is evidence for good acquisition intra-rater reliability of thyrohyoid

approximation and tongue thickness assessed in patients with Parkinson's disease (E. H. Oh et al., 2016).

There are different potential explanations for the different findings of this study compared to published reliability data. One aspect that likely impacted our study findings is the instrumentation. Our reliability data suggest that the pocket-sized Clarius<sup>TM</sup> system may not meet standards of image quality of more sophisticated instrumentation used in previous reliability studies (Y.-C. Chen et al., 2017; Hsiao et al., 2012; Huang et al., 2009; Macrae et al., 2012). The impact of instrumentation is further supported by the findings of measurement rather than acquisition reliability. Measurement reliability of pre-selected images of hyoid excursion and thyrohyoid approximation was insufficient. This indicates the scanning procedure and selection of images for measurement did not fully explain poor acquisition reliability for these measures. Notably, good measurement reliability for pre-selected images of tongue thickness and moderate to good measurement reliability for CSA of the floor of mouth muscles suggest that visualisation of motionless measures using Clarius<sup>TM</sup> may be clearer than movement-related measures. This mirrors findings of studies investigating reliability of videostroboscopic ratings of voice parameters that reported higher reliability for static compared to dynamic measures (Gelfer, 1998).

The findings of measurement reliability contrast with reliability outcomes documented in previous studies using larger ultrasound instrumentation. Prior data from our research laboratory suggest good intra-rater and moderate inter-rater measurement reliability (including image selection) of hyoid excursion assessed in five healthy adults (Macrae et al., 2012). Further, Chen and colleagues (2017) documented good image measurement reliability of hyoid excursion in 10 dysphagic patients. Good intra-rater reliability was reported for tongue thickness in 104 elderly subjects by Tamura and colleagues (2012); notably, tongue thickness was assessed coronally using a fixation device for the transducer. Yet, no information about inter-rater reliability is provided in this manuscript. Poor measurement reliability of hyoid excursion and thyrohyoid approximation in our study may indicate unreliable measurement techniques. However, this is unlikely, as measurement methods of hyoid excursion and thyrohyoid approximation used in this study are based on methods reported in studies that documented good reliability for hyoid excursion (Macrae et al., 2012) and thyrohyoid approximation (Huang et al., 2009). The measurement technique for hyoid excursion was the same as reported by Macrae and colleagues (2012) except that in the present study a line of best fit along the shadow of the hyoid was additionally used for facilitated identification of the

measurement points. The measurement methods for thyrohyoid approximation were based on images published by Huang and colleagues (2009); detailed measurement descriptions were not reported by these authors.

Discrepancies between our study results and published reliability data are also likely explained, in part, by differences regarding data analyses. Reliability analysis using ICCs is based on an analysis of variance; hence, it is critical to check that the assumptions for analysis are satisfied. However, it is not reported if assumptions were evaluated in published manuscripts (Y.-C. Chen et al., 2017; Hsiao et al., 2012; Huang et al., 2009; Macrae et al., 2012; Tamura et al., 2012); thus, some published findings may be questionable. Reliability can be calculated for single measures (Macrae et al., 2012) or for average measures (Hsiao et al., 2012; Huang et al., 2009; Shimizu et al., 2016). From a clinical point of view, good reliability is required for single measures rather than for averages. Reliability findings based on analysis using average measurements will likely be higher as compared to single measurements as average measurements are likely more reliable than single measurements (Hallgren, 2012; Shrout & Fleiss, 1979). Notably, while in our study all data were considered for analyses, only the best of three recordings was considered in the study by Chen and colleagues (2017). This likely increased reliability in their study.

This is the first study to evaluate whether any individual rater acquired measures with systematic differences compared to other raters such as that one rater systematically measured greater hyoid excursion compared to another rater. There is evidence for a systematic rater effect for several measures. Only for thyrohyoid approximation, the measurement difference across raters represents a large portion if compared to the mean thyrohyoid approximation across participants. Thus, for the other measures, the differences across raters may be less clinically relevant. Systematic rater differences suggest that raters interpreted the written measurement guidelines differently. Thus, more detailed description regarding the measurement technique for thyrohyoid approximation will be required for the guideline. Future research is required to systematically analyse training protocols based on such guidelines. Further, there was evidence for some systematic session differences. The size of these differences in measurements is potentially not large enough to be clinically relevant if considered in relation to the mean measurement. Thus, test-retest reliability was likely not confounded by a systematic change of rater performance over time due to factors such as learning.

This is the first study to explore whether reliability of tongue thickness differed across boluses with different fat content. Findings suggest that boluses with a higher fat content may be visualised more distinctly using ultrasound. Said differently, this may reflect that a bolus such as oil, which differs significantly in its acoustic impedance from the tongue muscle, may be visualised more clearly. In contrast, liquid may not strongly reflect ultrasound waves due to similar acoustic impedance compared to the tongue (Aldrich, 2007; Epstein & Stone, 2005; Kossoff, 2000). The use of apple sauce is standard in clinical swallowing assessment. Yet, administration of a high-fat bolus may be beneficial to achieve maximal reliability in assessment of tongue thickness.

Unlike previous reliability studies, this study evaluated the impact of different components of data acquisition on reliability. This information may guide development of future training programmes for clinicians. The findings suggest that the scanning procedure did not significantly impact reliability. However, image selection contributed to reliability. For all measures except for thyrohyoid approximation, intra- and inter-rater measurement reliability of pre-selected images was higher than measurement reliability that included image selection and measurement. For thyrohyoid approximation, the findings suggest that raters were more reliable if they performed measurements on self-selected, rather than on pre-selected images. This may indicate that raters required moving images to identify corresponding measurement points across images.

#### ***7.4.3. Limitations and Future Research***

Limitations of this research are important to acknowledge. The assumptions for statistical analyses were violated for some outcomes of the validity and reliability studies. Limitations specific to the validation study include exclusion of thyrohyoid approximation measurements from analyses due to poor videofluoroscopic visualisation of the thyroid cartilage. Imaging difficulties likely arose because cartilages are less radio-opaque than bony structures such as the hyoid (Mollenhauer et al., 2002). For data extraction using videofluoroscopy, an additional source of measurement error was introduced through manual calibration using external software. Calibration for ultrasound measurements was performed automatically by the system-based software. Future studies will benefit from the use of a three-dimensional calibration ball. A ball will reduce the impact of head rotation or head tilt during videofluoroscopy on calibration (Kahrilas, Lin, Logemann, Ergun, & Facchini, 1993). Although image selection and measurement techniques for videofluoroscopy were maximally

approximated to those for ultrasound, some adjustments for thyrohyoid approximation, as described previously, were required. Further, the frame rate of videofluoroscopy and ultrasound was not identical; it is unclear whether this impacted the findings.

Further limitations concern the technology used in this research. Results may have been impacted by diverse technical difficulties, such as connection problems between the ultrasound scanner and iPad. Due to this issue, numerous recordings were aborted and redone; prolonged sessions may have fatigued participants and examiners. In some sessions, selection of images for measurement was impeded due to difficulties with the scrolling function for video review. Other technical issues concerned the saving process of recorded ultrasound data which resulted in missing data for offline reliability assessment.

In conclusion, there was evidence of prior research suggesting that larger ultrasound equipment is valid and reliable in the assessment of swallowing measures such as hyolaryngeal excursion (Hsiao et al., 2012; Huang et al., 2009). Thus, this study aimed to evaluate whether similar findings would be revealed for a pocket-sized ultrasound device. The findings of this study indicate that the use of the pocket-sized Clarius™ system for evaluation of swallowing is not indicated at this time. Future research is needed to elucidate whether our study findings apply to the use of the Clarius™ system only or if they mirror true limitations of new pocket-sized ultrasound technology. Thus, research is needed to assess validity and reliability of other pocket-sized systems. Further, more research is needed to evaluate whether our data reflect limitations of ultrasound swallowing assessment also for more robust and expensive equipment. Future research is indicated to clarify essential requirements for standardised training recommendations in use of ultrasound in swallowing, as there is an absence in current published literature.

## **8. Assessment of the UES: A Systematic Review of Pharyngeal HRM/HRIM<sup>15</sup>**

### **8.1. Introduction**

Pharyngeal HRM provides objective pressure data in the assessment of the UES at rest and during swallowing (Jungheim, Schubert, et al., 2015; Knigge et al., 2014). With adjunctive impedance, information reflective of bolus flow during pharyngeal swallowing can be gained non-radiologically (Omari, Dejaeger, Van Beckevoort, Goeleven, De Cock, et al., 2011). Compared to prior manometric systems, the greater number of sensors allows for increased spatial resolution, which is specifically beneficial for evaluation of the UES (S. Meyer et al., 2012). Originally developed for measurement of oesophageal motility, HRM has been increasingly used in the evaluation of pharyngeal swallowing (Knigge et al., 2014). In the instrumental swallowing assessment, the use of HRM as a supplemental method to videofluoroscopy can provide objective temporal and magnitude data of UES physiology. Hence, pressure analysis can be critical for differential diagnosis (Knigge et al., 2014).

Methodological aspects of data acquisition and analysis may impact clinical interpretation of data. For example, for the width of the catheter in situ, it has been reported that pressure at the UES might be more affected with increasing catheter diameter (Nativ-Zeltzer et al., 2016). Further, an effect of the subjects' body position during the procedure on measurement parameters of the velopharynx and the UES in healthy adults has been documented in the literature (Rosen et al., 2018). As for the effect of topical anaesthesia on pharyngeal pressures, a double-blinded study reported a change in pharyngeal measurement parameters in healthy participants when topical anaesthesia was applied as compared to a no anaesthesia condition (Guiu Hernandez et al., 2017). For studies using HRIM, the conductivity of the bolus depends on its salinity (Gyawali et al., 2013) and on bolus consistency (Omari et al., 2006). Thus, methods need to be considered in the interpretation of findings in studies using pharyngeal HRM/HRIM. Since the use of pharyngeal HRM/HRIM is in the early stages, no

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<sup>15</sup> The content contained in Chapter 8 was published as Winiker K, Gillman A, Guiu Hernandez E, Huckabee M-L, Gozdzikowska K (2018). A systematic review of current methodology of high resolution pharyngeal manometry with and without impedance. *European Archives of Oto-Rhino-Laryngology*, 276(3), 631-645. The content is reprinted with permission of Elsevier.

methodological standards have yet been reached consensus for this application (Jungheim, Miller, & Ptok, 2013).

This review summarised and appraised the status quo of reported methodology of pharyngeal HRM/HRIM in adult populations and highlighted aspects that require attention for further development and optimal use of pharyngeal HRM/HRIM.

## **8.2. Materials and Methods**

### ***8.2.1. Protocol and Registration***

This review was registered in the international prospective register of systematic reviews on the 13<sup>th</sup> of March 2017 (Registration number: CRD42017059144)<sup>16</sup>. For reporting, guidelines of PRISMA (Moher et al., 2009), as well as AMSTAR (Shea et al., 2007) were followed.

### ***8.2.2. Eligibility Criteria***

Publications reporting the use of pharyngeal HRM or HRIM for swallowing or phonation assessment in adult populations (> 18 years) were included if they reported pharyngeal measures with or without additional report of measures of the UES. Further, documentation of methodology of data acquisition and analysis was required for inclusion. Studies using 3D HRM systems, water-perfused HRM, or catheters with less than 15 sensors, as well as manuscripts reporting only impedance data, were excluded. Eligibility for inclusion was restricted to publications in English, German, and Spanish as translation resources were not available. Manuscripts other than peer-reviewed journal articles, such as conference abstracts or reviews, were excluded. Records were included with no constraint regarding publication year.

### ***8.2.3. Information Sources***

Four electronic bibliographic databases were searched in and up to March 2017 including MEDLINE, EMBASE, CINAHL, and the Cochrane Library. To identify further relevant publications, the bibliographies of all selected publications for this review were screened by their title and tracking of citations via the website Google Scholar was performed.

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<sup>16</sup> Available from [https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=59144](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=59144)

#### **8.2.4. Search**

The search varied slightly according to requirements of the search databases. All search strings and keywords that were used are listed in *Appendix C*. As an example, the following represents the search strategy used in MEDLINE: 1. Deglutition/; 2. swallow\*.af.; 3. degluti\*.af.; 4. dysphagi\*.af.; 5. pharynx\*.af.; 6. Esophageal Sphincter, Upper/; 7. (upper esophageal sphincter or upper oesophageal sphincter or UES).af.; 8. impedance.af.; 9. Or/1-8, 10. HRM.af.; 11. High resolution manometry.af.; 12. Or/10-11; 13. 9 and 12.

#### **8.2.5. Study Selection**

Following the initial search, duplicates and records published in a language other than English, German, or Spanish were excluded. For the remaining articles, titles and abstracts were screened for inclusion based on keywords ('high resolution manometry'/'HRM' and/or 'impedance', 'pharynx'/'pharyngeal' and 'upper esophageal sphincter'/'UES'). A second-stage, full-text screening of the remaining publications was performed for further application of the eligibility criteria. Both first- and second-stage examinations were conducted by two independent researchers to minimise bias of individual raters. In the case of initial disagreement, discussion was undertaken to reach a consensus. Reference and citation checking were applied for the publication titles only and based on a reduced number of keywords including 'high resolution manometry'/'HRM' and 'impedance'.

#### **8.2.6. Data Collection Process**

In total, five reviewers were involved in data collection. Data from each article were extracted into a table by two independent reviewers. Agreement between raters was checked for parameters involving numerical or binary information (yes/no) and discussion was held to reach a consensus.

#### **8.2.7. Data Items**

Information was extracted based on the following five main categories:

1. General information about the publication (primary author's name, publication year, journal, and publication language),
2. Information about subjects involved in the study (number of healthy participants or patients, aetiology of dysphagia),



3. Data about the HRM/HRIM system and catheter (diameter, number of pressure sensors/impedance segments, spacing between sensors/segments, and measurement direction),
4. Information regarding methodological aspects of data acquisition (use of topical anaesthesia, including dose and application location, documentation/duration of an adjustment period after catheter placement, participants' position, bolus type/administration, bolus salinity for HRIM studies, application of a system-based measurement error correction (relevant only for studies using ManoScan™ system [Medtronic, Minneapolis]), and
5. Information about methodological aspects of data analysis (type of software, anatomical region of interest, and measurement parameters).

There are methodological aspects, such as the use of topical anaesthesia, which apply to studies using HRM and HRIM. Other methodological facets, such as the impact of bolus properties, differ across the two procedures and were analysed separately.

#### ***8.2.8. Level of Evidence and Methodological Quality Assessment of Individual Studies***

The level of evidence of each study was determined according to The Oxford Centre for Evidence-based Medicine - Levels of Evidence (Howick et al., 2009). Two items specific to the quality of data analysis - blinding and randomisation - were coded with a 'yes' or 'no' binary response. Report of inter- and/or intra-rater measurement reliability was assessed. As recommended in the literature, all studies were evaluated by two independent raters and disagreements were discussed to reach a consensus (Higgins et al., 2011).

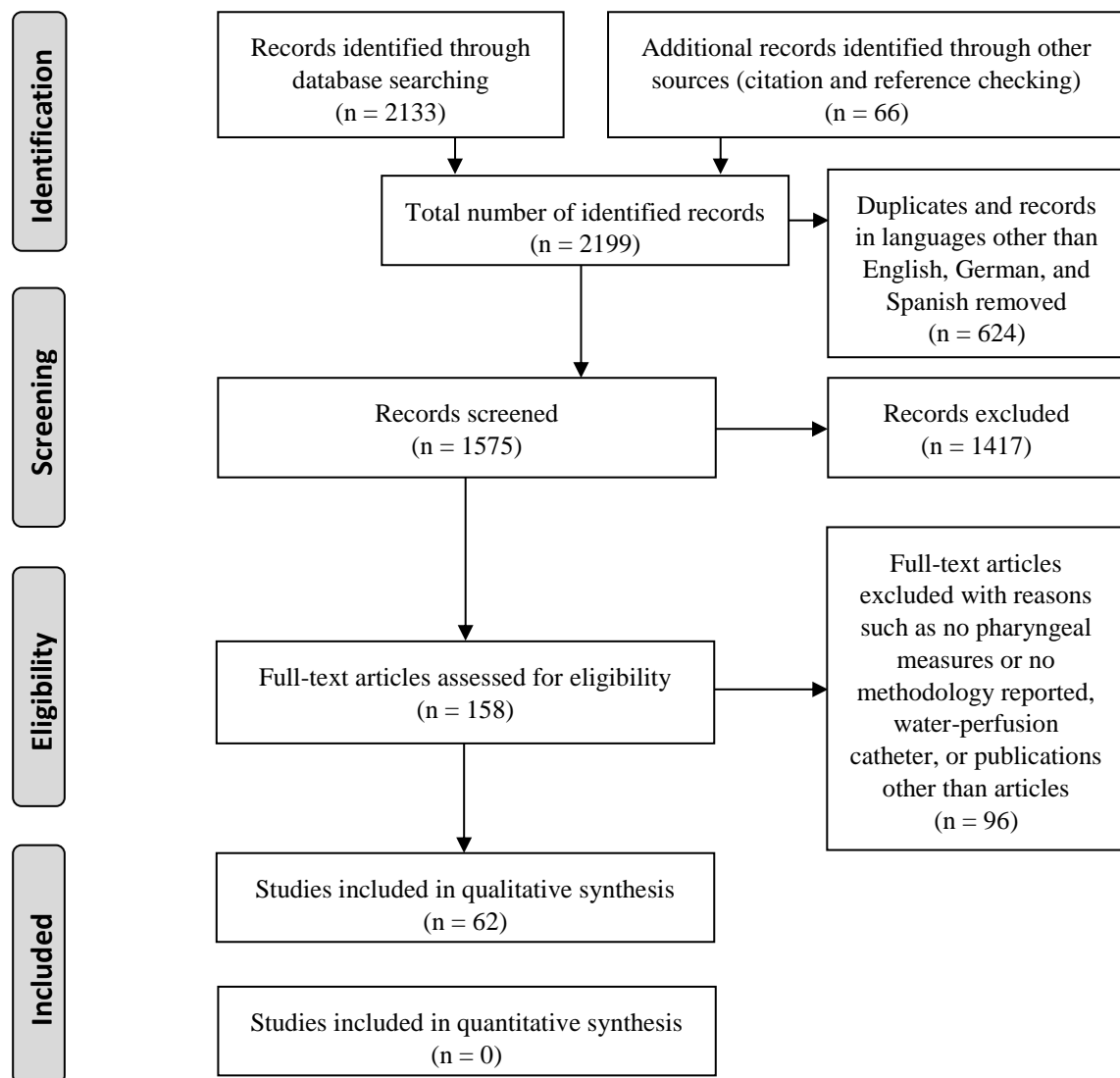
### **8.3. Results**

A meta-analysis could not be performed due to inconsistencies in reported methodology across studies and lacking documentation of methods.

#### ***8.3.1. Study Selection***

An initial search identified 2133 records; a further 66 manuscripts were identified later in the process (37 articles through reference checking, 29 papers through citation tracking). After removal of duplicates and records published in languages other than English, German, and Spanish, a total of 1575 abstracts remained, which were screened by the two raters. After screening, 1417 abstracts were excluded as they did not meet the inclusion criteria. Initial agreement regarding study selection was reached on 83%; following discussion, a consensus

was achieved on 100% of the abstracts. Ultimately, 62 publications met the eligibility criteria. Of these, 50 studies used pharyngeal HRM and 12 studies used HRIM. Information including reasons for exclusion is provided in the adapted PRISMA flow chart (Moher et al., 2009) (Figure 27).



**Figure 27.** Adapted PRISMA 2009 Flow Diagram.

### 8.3.2. General Information

The articles were published between 2006 and 2017, 93.5% in English, 6.5% in German; there were no Spanish manuscripts.

### **8.3.3. Results of Individual Studies**

For ease of reading, the reference formatting has been adapted for the results section. The superscript numbers refer to the numeration in Table 18. In-text references were only included for information that is not provided in Table 18.

#### **8.3.3.1. Subjects**

Manuscripts reported data on healthy adults (41.9%) and patients (32.3%); 24.2% of the articles documented data on both populations. A minority of publications (1.6%) did not provide any information on the subjects recruited. Aetiology of dysphagia included stroke<sup>12,21,22,24,25</sup>, Parkinson's disease<sup>2,11</sup>, ALS<sup>36,44</sup>, myotonic dystrophy<sup>14</sup>, Huntington's disease<sup>54</sup>, head and neck cancer<sup>48,62</sup>, achalasia<sup>32</sup>, as well as total laryngectomy<sup>1,27,50</sup>, or heterogeneous aetiologies<sup>3,8,18,33,34,38-40,52,53,55,57,59,60</sup>. Further studies recruited subjects after oesophageal replacement<sup>10</sup> or spinal cord surgery<sup>37</sup>.

#### **8.3.3.2. HRM System and Catheter**

The ManoScan<sup>TM</sup> HRM system was most commonly utilised (64.5%). The second most prevalently utilised system was Solar GI<sup>TM</sup> (Medical Measurement Systems/Laborie, Toronto) (19.4%), followed by inSIGHT<sup>TM</sup> (Sandhill Scientific, Milwaukee) (11.3%). The system used was not reported in 4.8% of the studies. Reports of nine different catheter diameters were found (Table 16). Importantly, 17.7% of all articles did not provide information about the catheter diameter. The number of pressure sensors ranged from 20 to 36, with 36 being the most commonly documented number of sensors (66.1%), followed by 25 sensors (11.3%), 32 sensors (9.6%), and 20 sensors (6.5%); 6.5% of studies using HRM or HRIM did not specify the number of pressure sensors. For the studies using HRIM, the number of impedance segments ranged from six to 18, with 12 segments being most prevalently reported (50%), followed by 18 segments (25%), and six segments (16.7%); 8.3% of the studies did not report the number of impedance segments. Of the studies using HRM, 72% documented a spacing of 1 cm between pressure sensors, 2% reported 0.75 cm, 12% had different spacing for different sensors and 14% did not provide information regarding the distance between sensors. Of all studies, the majority used catheters measuring pressure circumferentially (61.3%); a minority reported the use of catheters measuring unidirectionally (4.8%). In 32.3% of manuscripts, the measurement direction was not documented, one study utilised a catheter including some circumferential and some unidirectional sensors (1.6%).

**Table 16.** Reported catheter sizes

<b>Catheter diameter</b>	<b>Number of studies</b>	<b>Percentage of studies</b>
4.2 mm	19	30.6%
4.1 mm	1	1.6%
4 mm	10	16.1%
3.6 mm	2	3.2%
3.2 mm	5	8.1%
2.75 mm	5	8.1%
2.64 mm	3	4.8%
2.5 mm	1	1.6%
2 mm	4	6.5%

### 8.3.3.3. *Methodology of Data Acquisition*

Slightly more than half of the publications utilised topical anaesthesia (53.2%); 6.5% of the articles stated that no topical anaesthesia was used, and 40.3% of studies did not report whether topical anaesthesia was applied. In studies utilising topical anaesthesia, variable administration locations were documented including the nasal passage (33.3%), the catheter (3.1%), or combinations such as ‘nasal passage and catheter’ (24.2%), or ‘nasal passage, catheter, and oral gargle’ (24.2%). In 15.2% of the studies reporting the use of topical anaesthesia, readers were not informed about the application location. In total, three types of anaesthesia were specified including Lidocaine (69.7%), Lignocaine (18.2%), and Xylocaine (3.0%). A minority of 9.1% of studies did not report the type of anaesthetic used. Doses of topical anaesthesia varied among studies. For example, for Lidocaine, the doses ranged from 2% to 10% preparations. An adjustment period after catheter placement was reported in 53.2% of the papers<sup>3-9,11,14-17,21-31,33,34,38,39,41,51,55,56,58,59,61</sup> (durations ranging from five to 10 minutes). In 46.8% of the studies<sup>1,2,10,12,13,18-20,32,35-37,40,42-50,52-54,57,60,62</sup> the reader is not informed if an adjustment period was part of the protocol.

Regarding the positioning of the subjects during the study protocol, a sitting position was reported in 71.0% of the manuscripts and a supine position was documented less frequently (11.3%). In 17.7% of manuscripts, no information on positioning was provided. The following bolus types were documented to be used solely or in combination: dry swallows (22.6%), liquid

(91.9%), puree (27.4%), and solid (8.1%). Of the studies using HRIM, 91.7% reported use of a saline bolus while 8.3% did not provide information regarding whether saline was used. Of these studies reporting the use of saline, 36.4% provided information regarding salinity percentage. Table 17 summarises the number of studies using HRM/HRIM that provide sufficient data regarding methodological aspects of data acquisition to be replicated (Laine et al., 2007).

**Table 17.** Replicability of reported methodology of data acquisition

<b>Methodological aspect</b>	<b>Percentage of manuscripts providing sufficient information for replication</b>
Equipment (HRM system, catheter diameter, number of sensors, sensor spacing, and measuring direction)	58.1% (of all HRM/HRIM studies)
Topical anaesthesia (dose and application location)	38.7% (of all HRM/HRIM studies reporting the use of topical anaesthesia)
Salinity percentage of bolus	33.3% (of all HRIM studies)

*Note.* HRM = high-resolution manometry, HRIM = high-resolution impedance manometry

#### 8.3.3.4. *Methodology of Data Analysis*

For studies utilising HRM, the use of software intrinsic to the recording system was reported more frequently (56%) than the use of external software (Matlab™ [MathWorks, Natick]; 26%). A combination of both system built-in and external software was documented in 8% of the studies; a minority of the publications did not specify the type of software utilised (10%). For studies using HRIM, the majority documented the use of external software (e.g., Matlab™, AIMplot; 75%), whereas the application of the system-based software was documented only in one study (8.3%). No study reported the use of a combination of system-based and external software; 16.7% did not provide information regarding software used for analysis.

The ManoScan™ system requires correction of a system-based measurement error (Lamvik et al., 2016). In 22.5% of manuscripts, authors reported whether the required correction was applied<sup>4,20,22,24,26,43-46</sup>. In the remaining publications utilising the ManoScan™ system<sup>1,3,5-12,18,21,23,25,27-35,40,42,47-49,51,56,61</sup>, it was unclear if the correction was made and not reported, or if a potential error was present in the data.

In studies using HRM, a variety of definitions of the anatomical regions of interest were found. A frequently referenced definition for the velopharynx was “region of swallow-related pressure

change, just proximal to the area of continuous nasal cavity quiescence and extending 2 cm” (McCulloch et al., 2010). In contrast, other authors defined this region as “the boundary between the velopharynx and the meso-hypopharynx”, highlighted during verbalisation of “papapa” (Matsubara et al., 2016). Various terms were found when referring to the anatomical region between velopharynx and UES, in addition to differing definitions. In some studies, this area was considered as a single region and referred to using terms such as ‘pharynx’<sup>1,2,21-23,36</sup>, ‘tongue base’<sup>5-7,13-16,18,19,31,33,40</sup>, ‘mesopharynx’<sup>8,11,25,27,48</sup>, or ‘epiglottis’<sup>32,42</sup>. In other manuscripts, the anatomical region between velopharynx and UES was divided into sub-regions, such as ‘tongue base’ and ‘low(er) pharynx’<sup>17,37-39,41</sup>.

For studies using HRM, measurement parameters reported for the pharynx included pressure amplitude, documented in 90% of the studies. Of these studies, the most frequently reported amplitude measure (91.1%) was maximum/peak pressure<sup>3,4,6-19,21-24,26-28,30-35,37-46,48,50</sup>. Various types of timing measures were documented in 52% of the manuscripts. These included one or a combination of the following temporal measures: contraction duration (including ‘Kontraktionszeit’ in German)<sup>3,5-8,10-12,14,15-17,21,23,26,27,31-34,37-42</sup> (100%), rise and/or fall time<sup>3,8,17,32,37,38,39,41,42</sup> (34.6%), and time intervals<sup>17,41</sup> (7.7%). Further, 16% of publications reported an anatomical length measure<sup>6,14-16,28,43,45,46</sup> such as the distance from the nostril to the maximum pressure point of the pharynx. Apart from these unidimensional amplitude, timing and distance measures, 52% of the reports documented other types of parameters including multidimensional measures characterised by more than one unit. Of the articles documenting other types of measures, 57.7% reported rate of pressure generation (including ‘Geschwindigkeit der Kontraktionswelle’ reported in German)<sup>3,6,7,8,14,15,16,17,23,26,27,31,33,34,41</sup>, 53.8% reported various types of integral measures<sup>2,3,7,11,25,27,33-35,38-41,49</sup>, 19.2% documented velocity of the contraction wave<sup>2,17,29,33,34</sup>, and 7.7% documented pressure gradients<sup>31,33</sup>. For the UES, 88% of the studies published a type of amplitude measure such as UES pre- or post-opening/nadir pressure<sup>3,5-8,12,14-18,23,26,27,31,33-35,37-39,41</sup> (50%), a type of minimum/nadir UES pressure<sup>2-8,11,12,17,18,25,27,31,33,34,37-39,41,49</sup> (47.7%), residual pressure<sup>1,10,14-16,21-24,26,32,42</sup> (27.3%), resting pressure<sup>1,2,14-16,21,28,40,44</sup> (20.5%), or basal pressure<sup>24,25,32,36,42,49</sup> (13.6%). In 68% of the publications, a timing measure was documented including UES activity time<sup>3,7,8,12,14-17,27,33,34,37-39,41</sup> (44.1%), UES relaxation duration/interval (including report of ‘Relaxationszeit’ in German)<sup>4,10,14-16,21,23-26,32,40,42,49</sup> (41.2%), nadir UES duration/UES minimum pressure duration<sup>3,7,8,11,17,27,37-39,41</sup> (29.4%), or UES opening duration<sup>6,18,31,33</sup> (11.8%). Length measures<sup>28,32,35,42,43,45,46</sup> such as the distance from the nostril to the maximum pressure point at

the UES were documented in 14% of the reports. Measures other than amplitude and timing were published in 24% of the manuscripts and included measures such as integral measures<sup>3,7,8,25,27,33-35,40</sup> (75%), coefficient of variation<sup>11</sup> (8.3%), or deglutitive sphincter resistance<sup>4</sup> (8.3%). The variation in these timing measures may reflect differences in both measures and terminologies for similar or identical parameters.

The same parameters, according to the terminology used, were measured differently across studies. As an example, the measurement method defining start and endpoint of the ‘UES relaxation duration/interval’ was defined in one manuscript as “from onset at the point of departure from half the baseline to the offset at the return to half baseline pressure” (T. Lee et al., 2017). In another study, the start of the measurement period was specified as “a pressure drop by 10%” of the most central UES sensor, and the endpoint was determined “when the same pressure was reached again with the arrival of the pharyngeal contraction wave” (Jungheim, Schubert, et al., 2015)<sup>17</sup>. The measurement period for UES relaxation duration was not only defined differently across studies, but the choice of sensors on which to base the measurement differed as well.

Findings of HRIM will be reported descriptively; a discussion of existing pressure flow parameters goes beyond the scope of this review. In respect to pharyngeal impedance technology, the focus of HRIM analysis was on impedance-only parameters (e.g., nadir impedance<sup>51,52,61</sup>, flow interval<sup>52,53,57,58,60,61,62</sup>, ratio of nadir impedance to post-swallow impedance<sup>52,57,58,62</sup>), measures linking pressure and impedance data in a synergistic way (e.g., time from nadir impedance to peak pressure<sup>51-53,57,58,60-62</sup>, pressure at nadir impedance<sup>52,53,58,60-62</sup>) and composite parameters representative for global dysfunction which have been validated against instrumentations, such as videofluoroscopy (e.g., Swallow Risk Index<sup>52,57,59-62</sup>). Among the studies considered for this review, impedance data was documented as a percentage of incomplete versus complete bolus transit in one article only. However, there was insufficient information provided for this measure to be replicated<sup>54</sup>. Further, qualitative visual analysis of the impedance contour plots was documented in two studies<sup>55,56</sup>. Standardised external

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<sup>17</sup> Original publication language: “Bestimmung anhand des “zentralen Sensors” im oÖS. Ein Druckabfall um 10% markierte den Beginn der Relaxationszeit, das Ende wurde bei Wiedererreichen des gleichen Druckes mit dem Eintreffen der pharyngealen Kontraktionswelle definiert.”

software (e.g., AIMplot) was predominantly used, allowing report of similar parameters across publications<sup>51-53,57,58,60-62</sup>.

#### 8.3.3.5. *Level of Evidence and Methodological Quality Assessment of Individual Studies*

The majority of the included articles (74.2%) were rated as case-series (level 4), 24.2% of publications were case-control studies (level 3b), and one single study (1.6%) was classified as an expert opinion (level 5) (Howick et al., 2009). In regard to data analysis, randomisation was reported in 12.9%<sup>3,8,34,47,53,57,59,61</sup> and blinding in 17.7%<sup>11,12,21,39,52,55,56,59,60,61,62</sup> of the publications. A minority of publications using HRM provided data on inter- or intra-rater measurement reliability (10%), whereas the percentage was considerably higher (50%) in studies using HRIM. A final 100% consensus was reached between the two raters for all items considered.



**Table 18.** Reported methodology of data acquisition and analysis

In-text reference number	General	Subjects	Equipment		Methodology of data acquisition			Methodology of data analysis		Level of evidence
	First author (year); language	Number of healthy subjects; patients	System (HRM; HRIM); system name	Catheter Diameter; measuring direction; number of pressure sensors; sensor spacing; impedance (number of segments)	Body Position	Anaesthesia Use (type; dose; application location)	Bolus Consistency; use of saline	Software	Reliability reports	
1	Arenaz Bua, Rydell, Estin, and Olsson (2016); English	0; 13	HRM; ManoScan™	4.2 mm; NR; 36; 1 cm	seated	Yes (Xylocaine; 2%; NR)	Liquid; NA	NR	NR	4
2	Derrey et al. (2015); English	0; 16	HRM; MMS	4 mm; circumferential.; 36; 1 cm	NR	NR	Liquid; NA	system-based	NR	3b
3	Geng et al. (2013), English	16; 61	HRM; ManoScan™	4 mm; circumferential.; 36; 1 cm	seated	Yes (Lidocaine; 2%; nasal/catheter)	Dry/Liquid/ Puree; NA	Matlab™	NR	4
4	Ghosh et al. (2006); English	75; 0	HRM; ManoScan™	4.2 mm; circumferential.; 36; 1 cm	supine	NR	Dry/Liquid; NA	system-based/ Matlab™	NR	4
5	Hammer et al. (2014); English	8; 0	HRM; ManoScan™	2.75 mm; circumferential.; 36; 1 cm	seated	Yes (Lidocaine; 2%; nasal/catheter)	Dry; NA	Matlab™	NR	4
6	Hoffman, Ciucci, Mielens, Jiang, and McCulloch (2010); English	12; 0	HRM; ManoScan™	4 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%/4%; nasal/ catheter/gargle)	Dry/Liquid; NA	Matlab™	NR	4

7	Hoffman et al. (2012); English	14; 0	HRM; ManoScan™	4 mm; circumferential; 36; 1 cm	NR	Yes (Lidocaine; 2%/4%; nasal/catheter/gargle)	Liquid; NA	Matlab™	NR	4
8	Hoffman, Jones, et al. (2013); English	0; 30	HRM; ManoScan™	4 mm; NR; 36; NR	seated	Yes (Lidocaine; 2%; nasal/catheter)	Liquid/Puree ; NA	Matlab™	unclear	4
9	Hutcheson, Hammer, Rosen, Jones, and McCulloch (2017); English	2; 0	HRM; ManoScan™	2.75 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%; nasal)	Liquid; NA	Matlab™	NR	4
10	Jiang et al. (2017); English	0; 1	HRM; ManoScan™	NR; circumferential; 36; NR	seated	NR	NR; NA	system-based	NR	4
11	Jones and Ciucci (2016); English	26; 26	HRM; ManoScan™	2.75 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%; nasal)	Liquid; NA	Matlab™	Previously reported	3b
12	Juan et al. (2013); English	0; 1	HRM; ManoScan™	2.5 mm; circumferential; 36; 1 cm	NR	Yes (Lidocaine; 2%; nasal)	Liquid; NA	Matlab™	NR	4
13	Jungheim, Miller, Kuhn, and Ptok (2013); German	0; 8	HRM; Solar GI™ (MMS)	2 mm; unidirectional; 20; 0.75 cm, distal sensor 5 cm	seated	NR	NR; NA	system-based	NR	4
14	Jungheim, Kuhn, et al. (2015); German	0; 2	HRM; Solar GI™	2 mm; unidirectional; 20; 0.75 cm, distal sensor 5 cm	seated	No	Liquid; NA	system-based	NR	4
15	Jungheim, Schubert, et al. (2015); German	29; 0	HRM; Solar GI™	2 mm; unidirectional; 20; 0.75 cm, distal sensor 5 cm	seated	No	Liquid; NA	system-based	NR	4

16	Jungheim, Kallusky, and Ptok (2017); German	10; 0	HRM; Solar GI™	2 mm; NR; 20; 0.75 cm, distal sensor 5 cm	seated	No	Liquid; NA	system-based	NR	4
17	C. K. Kim et al. (2015); English	10; 0	HRM; inSIGHT™	NR; circumferential; 32; 1 cm	seated	Yes (Lidocaine; 2%/10%; nasal/catheter)	Liquid; NA	system-based	NR	4
18	Knigge et al. (2014); English	0; 3	HRM; ManoScan™	4 mm; NR; 36; NR	NR	Yes (Lidocaine; 2%; nasal)	Dry/Liquid; NA	NR	NR	5
19	Knigge and Thibeault (2016); English	0; 37	HRM; NR	NR	NR	NR	Liquid; NA	NR	NR	4
20	Lamvik et al. (2016); English	NR; 0	HRM; ManoScan™	2.75 mm/4.2 mm; NR; 36; NR	NR	NR	Dry/Liquid; NA	system-based/Matlab™	NR	4
21	Lan, Xu, Dou, Wan, Yu, et al. (2013); English	0; 30	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%; nasal)	Liquid/Puree ; NA	system-based	NR	3b
22	Lan et al. (2015); English	0; 24	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	NR	Liquid/Puree ; NA	system-based	NR	4
23	Lan et al. (2017); English	34; 0	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	NR	Liquid/Puree ; NA	system-based	NR	4
24	T. H. Lee, Lee, Hong, Lee, Jeon, Kim, Kim, Cho, Kim, Cho, Park, et al. (2014); English	31; 122	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	NR	Liquid; NA	system-based	unclear	3b
25	T. Lee et al. (2017); English	0; 36	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%; nasal)	Liquid; NA	Matlab™	NR	4

26	Lin et al. (2014); English	34; 0	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	NR	Liquid/Puree ; NA	system-based	NR	4
27	Lippert et al. (2016); English	6; 6	HRM; ManoScan™	4.2 mm; NR; 36; NR	seated	Yes (Lidocaine; 2%; catheter)	Liquid; NA	Matlab™	NR	3b
28	Matsubara et al. (2014); English	30; 0	HRM; ManoScan™	2.64 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 4%; nasal/ catheter/gargle)	Dry/Liquid; NA	system-based	NR	4
29	Matsubara, Kumai, Samejima, and Yumoto (2015); English	30; 0	HRM; ManoScan™	2.64 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%/4%; nasal/ catheter/gargle)	Dry/Liquid; NA	system-based	Yes	4
30	Matsubara et al. (2016); English	26; 0	HRM; ManoScan™	2.64 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%/4%; nasal/ catheter/gargle)	Liquid; NA	system-based	NR	4
31	McCulloch et al. (2010); English	7; 0	HRM; ManoScan™	4 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%/4%; nasal/ catheter/gargle)	Liquid; NA	system-based	NR	4
32	Menezes et al. (2015); English	0; 60	HRM; ManoScan™	NR; NR; 36; 1 cm	NR	NR	Liquid; NA	system-based	NR	4
33	Mielens et al. (2011); English	12; 3	HRM; ManoScan™	4 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%/4%; nasal/ catheter/gargle)	Liquid; NA	Matlab™	NR	3b
34	Mielens, Hoffman, Ciucci, McCulloch, and Jiang (2012); English	12; 13	HRM; ManoScan™	4.1 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%/4%; nasal/ catheter/gargle)	Liquid; NA	system-based/ Matlab™	NR	3b
35	Nativ-Zeltzer et al. (2016); English	44; 0	HRM; ManoScan™	2.75 mm; circumferential; 36; 0.75 cm	seated	Yes (NR; NR; nasal)	Liquid/Puree /Solid; NA	system-based	NR	4

36	Noh et al. (2010); English	0; 1	HRM; NR	NR	supine	NR	Liquid; NA	system-based	NR	4
37	Y. Oh, Lee, and Ryu (2015); English	0; 1	HRM; InSIGHT™	NR; NR; NR; 1 cm	seated	NR	Dry/Liquid; NA	NR	NR	4
38	Park, Oh, and Ryu (2016); English	0; 40	HRM; InSIGHT™	NR; circumferential; 32; 1 and 2 cm	seated	Yes (Lidocaine; 2%/10%; nasal/catheter)	Liquid; NA	system-based	Yes	4
39	Park, Shin, and Ryu (2017); English	0; 53	HRM; InSIGHT™	NR; circumferential; 32; 1 and 2 cm	seated	Yes (Lidocaine; 2%/10%; nasal/catheter)	Liquid/Puree; NA	system-based	Yes	3b
40	C.-H. Park et al. (2017); English	33; 120	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	NR	Liquid; NA	system-based/Matlab™	Yes	3b
41	Ryu et al. (2016); English	10; 0	HRM; InSIGHT™	NR; circumferential; 32; 1 cm	seated	Yes (Lidocaine; 2%/10%; nasal/catheter)	Dry/Liquid/Puree/Solid; NA	system-based	NR	4
42	Silva et al. (2013); English	40; 0	HRM; ManoScan™	NR; NR; 36; 1 cm	seated	NR	Liquid; NA	system-based	NR	4
43	Takasaki et al. (2008); English	33; 0	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	supine	NR	Dry/Liquid; NA	system-based	NR	4
44	Takasaki, Umeki, Enatsu, et al. (2010); English	0; 1	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	supine	Yes (NR; NR; nasal)	Dry; NA	system-based	NR	4
45	Takasaki et al. (2011); English	18; 0	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	supine	Yes (NR; NR; nasal)	Dry/Liquid; NA	system-based	NR	4
46	Umeki et al. (2009); English	33; 0	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	supine	NR	Dry; NA	system-based	NR	4

47	Walczak, Jones, and McCulloch (2017); English	10; 0	HRM; ManoScan™	2.75 mm; circumferential; 36; 1 cm	seated	Yes (Lidocaine; 2%; nasal/catheter)	Liquid; NA	Matlab™	No	4
48	Yamaguchi et al. (2017); English	0; 10	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	supine	NR	Liquid; NA	system-based	NR	4
49	Yoon et al. (2014); English	26; 0	HRM; ManoScan™	4.2 mm; circumferential; 36; 1 cm	seated	NR	Liquid/Puree ; NA	Matlab™	NR	4
50	Zhang et al. (2016); English	11; 30	HRM; Solar GI™ (MMS)	3.6 mm; NR; 25; 1 cm	seated	Yes (Lignocaine; 10%; NR)	Liquid; NA	NR	NR	3b
51	Doeltgen, Omari, and Savilampi (2016); English	11; 0	HRIM; ManoScan™	4.2 mm; circumferential; 36; 1 cm; impedance (18)	NR	NR	Liquid; Yes	Matlab™	NR	4
52	Ferris et al. (2015); English	8; 40	HRIM; Solar GI™	3.2 mm; NR; 25; 1 cm; impedance (12)	seated	Yes (Lignocaine; NR; NR)	Liquid/Puree /Solid; Yes	Matlab™	NR	3b
53	Hoffman, Mielens, et al. (2013); English	0; 25	HRIM; Solar GI™	3.2 mm; NR; 25; 1 cm; impedance (12)	seated	Yes (Lignocaine; NR; nasal)	Liquid/Puree /Solid; No	Matlab™	unclear	4
54	T. H. Lee et al. (2012); English	26; 1	HRIM; Sandhill Scientific Instruments	4 mm; NR; 32; NR; impedance (6)	seated	NR	Liquid/Puree ; Yes	system-based	NR	4
55	T. H. Lee, Lee, Park, et al. (2014); English	26; 10	HRIM; Sandhill Scientific Instruments	4 mm; circumferential /unidirectional; 32; NR; impedance (6)	seated	NR	Liquid; Yes	NR	Yes	3b

56	T. H. Lee, Lee, Hong, Lee, Jeon, Kim, Kim, Cho, Kim, Cho, Kim, et al. (2014); English	33; 104	HRIM; ManoScan™	4.2 mm; circumferential; 36; 1 cm; impedance (18)	seated	NR	Liquid; Yes	NR	NR	3b
57	Omari, Papathanasopoulos, et al. (2011); English	8; 18	HRIM, NR	NR	NR	NR	Liquid/Puree ; Yes	Matlab™	Yes	4
58	Omari, Kritas, and Cock (2012); English	20; 0	HRIM; Solar GI™	3.2 mm; NR; 25; 1 cm; impedance (12)	seated	Yes (Lignocaine; NR; NR)	Liquid/Puree ; Yes	Matlab™	NR	4
59	Omari, Dejaeger, et al. (2012); English	8; 18	HRIM; Solar GI™ (MMS)	3.2 mm; NR; 25; NR; impedance (12)	NR	NR	Liquid/Puree ; Yes	Matlab™	Yes	3b
60	Omari et al. (2013); English	0; 40	HRIM; Solar GI™ (MMS)	3.2 mm; NR; 25; 1 cm; impedance (12)	seated	Yes (Lignocaine; NR; NR)	Liquid/Puree /Solid; Yes	Matlab™	Yes	4
61	Omari, Savilampi, et al. (2016); English	5; 0	HRIM; ManoScan™	4.2 mm; circumferential; 36; 1 cm; impedance (18)	NR	No	Liquid; Yes	Matlab™	Yes	4
62	Szczesniak et al. (2015); English	16; 16	HRIM; Solar GI™ (MMS)	3.6 mm; NR; 25; 1 cm; impedance (12)	seated	Yes (Lignocaine; 10%; nasal)	Liquid; Yes	Matlab™	Yes	3b

*Note.* HRM = high-resolution manometry, HRIM = high-resolution impedance manometry, NR = not reported, NA = not applicable, Level of evidence was determined according to The Oxford Centre for Evidence-based Medicine Levels of Evidence (Howick et al., 2009)

## **8.4. Discussion**

The use of HRM/HRIM in the assessment of pharyngeal swallowing is rapidly increasing in research and clinical practice. Importantly, this technology is used as a diagnostic tool in patient populations with dysphagia. Critical decisions such as surgical interventions for UES impairment, may be based on these assessments. Further, rehabilitation progress may be assessed based on pressure findings. Thus, appropriate use of this instrumentation, including refined methodology, is paramount. This review highlights substantial variability in methodology of data acquisition and data analysis in studies using HRM/HRIM.

### ***8.4.1. Methodology of Data Acquisition***

Methodological variability was apparent regarding data acquisition for studies using pharyngeal HRM and HRIM. The use of different HRM systems and different catheter features including number of sensors, sensor spacing, or measurement direction was highlighted in the systematic review. Future data regarding the impact of such methodological aspects will clarify limitations in data comparison across studies if different equipment was used. Nine catheter sizes were documented across the studies involved in this review. Since the size of the catheter may impact data, comparability across studies using different catheter sizes is limited. Further, methodological variability was apparent regarding application of an adjustment period following catheter placement. Future research is required to evaluate the impact of the adjustment period on data since no systematic study has yet been completed. Additionally, clarification of whether different durations of adjustment periods impact data is required. This systematic review revealed that the use of topical anaesthesia is common practice in studies using pharyngeal HRM/HRIM. While there is data to suggest that topical anaesthesia may impact pressure data (Guiu Hernandez et al., 2017), there is evidence that the use of anaesthesia does not improve comfort during the procedure of pharyngeal HRM whether using a 2.75 mm HRM catheter (Guiu Hernandez et al., 2017) or a 4.2 mm HRIM catheter (Kwong, 2018). Thus, it is recommended that clinicians carefully weigh the influence of anaesthesia on pressure data against questioned benefits of comfort. This review further revealed broad variation in dose and application location of topical anaesthesia across studies. Thus, future research is necessary to elucidate whether the impact of anaesthesia on pressure depends on dosage and application location. While participants obtained an upright position during the HRM/HRIM procedure in some studies, other studies reported a supine position. Caution is warranted when comparing data from studies reporting different body positions of the subjects during assessment, as pressure may be affected differently. Regarding studies using HRIM, a saline bolus was used



in the majority of manuscripts; lacking report of salinity percentage was common. Ongoing research is needed to clarify how salinity affects the data.

#### **8.4.2. Methodology of Data Analysis**

This review also highlights variability of methodology regarding data analysis. The potential impact of methodology of data analysis on study results needs to be incorporated in the interpretation of outcomes. For example, for studies using the most commonly reported ManoScan™ system, it needs to be appreciated that data might vary depending on whether corrections of the system-based measurement errors were applied (Lamvik et al., 2016). The use of system-based software was the most commonly reported in studies using HRM. However, this software was originally developed for evaluation of the oesophagus and needs to be critically evaluated if used in the context of pharyngeal swallowing. For example, the ManoScan™ system offers built-in software (ManoView™), which provides automated analysis mainly for the oesophagus. However, for the pharynx and UES, only limited automated analyses are embedded into the recording system. Further, poor agreement between automated and manual analysis using this software has been reported for some UES parameters (T. H. Lee, Lee, Hong, Lee, Jeon, Kim, Kim, Cho, Kim, Cho, Park, et al., 2014). In contrast, customised methods using external software offer pharynx-specific analyses. However, the various analysis techniques utilised in research and clinical practice restrict the comparability of data (Jungheim, Miller, & Ptok, 2013). Further development of pharynx-specific system-based software or open-access external software, such as *Swallow Gateway™* (Omari, 2018), will contribute to facilitated implementation of HRM/HRIM into clinical practice and to enhanced international collaborations and comparability of data across research laboratories.

Regarding measurement parameters, differing terminology, definitions of anatomical regions of interest and measurement parameters, and varying measurement methods limit comparisons across studies considerably. Comprehension of which measurement parameters are most significant for differential diagnosis of dysphagia is relevant for future application of HRM/HRIM. Efforts towards a more standardised terminology might contribute to improved comparisons across studies and facilitate communication across research laboratories and clinical institutions. For oesophageal manometry, the Chicago Classification was developed for application of standardised metrics and to provide guidance on classification of disorders (Kahrilas et al., 2015). Similar guidelines for pharyngeal HRM may contribute to facilitated cooperation across institutions.

Interestingly, the majority of studies included for this review were published by five research laboratories. Considering this fact, the large variability in reported methodology is even more striking. Some observed variability in methodology within research groups arose from inconsistent reporting, such as whether topical anaesthesia was used. Hence, it is not clear whether a single research team actually used different methodology across different studies. However, observed methodological differences within research groups may also highlight that pharyngeal HRM/HRIM in swallowing assessment remains in the developmental stage.

#### ***8.4.3. Reporting Methodology***

The impact of methodological aspects of data acquisition and analysis emphasises the need for detailed reports of methodology in publications using HRM/HRIM. This review revealed a remarkably high number of manuscripts lacking documentation of methodology. Insufficient methodological information devalues study results, as interpretation of the data is restricted. Explicit methodological documentations are strongly suggested, enabling readers to understand published data in the context of the selected methodology. Development of guidelines defining minimal standards for reporting will enhance the comparability of data across studies. Further, detailed methodological reports are required to allow for replication and comparison of data across studies. A particular emphasis on the status quo of reporting reliability is warranted. The number of HRM studies not reporting measurement reliability is striking. Importantly, studies using HRIM more frequently report reliability analyses; however, reliability reporting should be standard in future publications for studies using either HRM or HRIM. Further, documentation of markers of methodological quality, including blinding and randomisation of data analysis, is warranted in future publications.

#### ***8.4.4. Limitations and Future Research***

Limitations of this review are acknowledged. The search was limited to published articles and to the languages English, German, and Spanish. Evaluation of reported methodology of pharyngeal HRM/HRIM in manuscripts published in further languages will reveal additional information about the current practice using this instrumentation. Reference lists and citations were screened for the words ‘high resolution manometry/HRM’ and ‘impedance’ in their title, only. Analysis of combined measures of pressure and impedance, as well as inclusion and review of impedance-only studies, should be reviewed in future publications as these reports were not considered in the present work. Due to the variability of terminologies, definitions, and measurement methods of the parameters of interest, a meta-analysis was not feasible.

In conclusion, a thorough evaluation of the existing literature is required as a foundation for the development of pharyngeal HRM/HRIM involving the formulation of methodological standards. Hence, this systematic appraisal of the status quo of published research is a contribution to ongoing efforts towards an optimised use of pharyngeal HRM/HRIM. Publications providing detailed reports of methodological aspects of data acquisition and analysis add valuable information to an increasing body of research, which is the base from which future developments arise. Some aspects of methodology such as system-based analysis software is inherently related with system products. Thus, collaboration between manufacturers and HRM users, including researchers and clinicians, is essential. With continuous development of methodological standards, ongoing exploration of validity and reliability of pharyngeal HRM/HRIM is critical. Sound validity and reliability are the foundation for optimal use of HRM/HRIM as a diagnostic tool for pharyngeal swallowing. Further, validity and reliability are the basis for establishment of normative data and exploration of topics such as clinical training.

Increased understanding of the impact of methodology of data acquisition and analysis on pressure and impedance data will contribute to refined decision-making process regarding methodology in future research. With clear evidence that significant variability is incorporated into methods for clinical research, there is a mandate for development of internationally accepted clinical assessment and analysis standards. Such standards of methodology will be necessary for development of best practice in the use of pharyngeal HRM/HRIM.

### **PART III: BEHAVIOURAL STUDY**

## **9. Behavioural Manipulation of the UES**

### **9.1. Introduction**

Tone is constantly present within the UES at rest, facilitating a functional barrier between the pharynx and oesophagus (Lang, 2013; S. Singh & Hamdy, 2005). Manometrically, this barrier can be measured as an area of high pressure (Lang, 2013). Adequate UES resting pressure is relevant for airway protection from potential refluxate and inhibits passive suction of air into the oesophagus during inspiration (Jungheim et al., 2014b; S. Singh & Hamdy, 2005). During pharyngeal swallowing, UES opening depends on timely and sufficient pressure relaxation (Jungheim et al., 2014b; S. Singh & Hamdy, 2005; Sivarao & Goyal, 2000). Impaired pressure relaxation may result in impeded bolus flow into the oesophagus and in decreased swallowing safety and efficiency.

UES pressure relaxation during swallowing is one component of the stereotyped sequence of events which constitutes pharyngeal swallowing. Historically, pharyngeal swallowing was considered to be a reflex (Ertekin & Aydogdu, 2003; Humbert & German, 2013; Vasant & Hamdy, 2013). It is now recognised that swallowing is a highly complex and dynamic function, controlled not only by the brainstem but also by diverse cortical and subcortical structures (Ertekin & Aydogdu, 2003; Humbert & German, 2013; A. J. Miller, 2013). Involvement of supratentorial structures, such as sensorimotor cortical areas, in the neural control of swallowing (Humbert & German, 2013; Michou & Hamdy, 2009) offers increased potential for purposeful manipulation of pharyngeal swallowing. There is research documenting behaviourally altered UES pressure during performance of swallowing manoeuvres (Doeltgen et al., 2017; Hiss & Huckabee, 2005; Hoffman et al., 2012; Huckabee et al., 2005; Takasaki et al., 2011; Witte et al., 2008). For example, it was reported that in healthy subjects, the duration of pressure related intra-swallow UES opening was prolonged during effortful swallowing (Hiss & Huckabee, 2005; Hoffman et al., 2012) and during execution of the Mendelsohn manoeuvre (Hoffman et al., 2012), a technique involving purposeful prolongation of swallowing related laryngeal movement (Logemann & Kahrilas, 1990). Both manoeuvres involve biomechanical alterations of pharyngeal swallowing, such as reduced hyolaryngeal excursion during effortful swallowing due to pre-swallow elevation of the hyolaryngeal complex (Bülow et al., 1999), or prolonged hyoid displacement during execution of the Mendelsohn manoeuvre (Inamoto et al., 2018). Further, altered pharyngeal pressure has been documented for effortful swallowing (Doeltgen et al., 2017; Huckabee et al., 2005; Takasaki

et al., 2011; Witte et al., 2008) and the Mendelsohn manoeuvre (Bodén et al., 2006; Doeltgen et al., 2017; Hoffman et al., 2012).

While the UES can be *indirectly* influenced during execution of the Mendelsohn manoeuvre and effortful swallowing, it is unknown whether pressure at the UES can be *directly* modulated. However, some individuals present with UES dysfunction characterised by isolated impaired UES relaxation in the absence of reduced hyolaryngeal excursion and impaired pharyngeal pressure generation. Because of this, specific treatment for impaired UES relaxation is required. Current treatment options including the Mendelsohn manoeuvre or effortful swallowing alter different aspects of swallowing; this could create a negative impact on swallowing. Thus, it is critical to understand whether pressure at the UES can be more directly targeted without changing pharyngeal pressure.

This exploratory research investigated the capacity of healthy adults to behaviourally modulate pressure at the UES. A study in healthy subjects allows for edification of the capacity for behavioural manipulation without confounding effects of neural injury. Specifically, this research questioned if UES resting pressure could be volitionally increased and decreased in the absence of swallowing (Exploratory Study 1), and if pressure related UES opening during swallowing could be purposefully prolonged (Exploratory Study 2). It was hypothesised that healthy subjects would be able to behaviourally modulate pressure at the UES following intensive biofeedback training; pressure modulation at the UES would be achieved without significant alteration of pressure in the pharynx as reported for effortful swallowing and for the Mendelsohn manoeuvre.

## **9.2. Exploratory Study 1: Behavioural Modulation of UES Resting Pressure**

### **9.2.1. Materials and Methods**

#### **9.2.1.1. Participants**

This proof of concept study recruited six participants to investigate the capacity of healthy participants for behavioural pressure modulation. Since there were inadequate data for sample size calculation, the sample size was based on another study of this laboratory that investigated behavioural modulation of pharyngeal swallowing and reported significant results (Lamvik et al., 2015). Participants were recruited via written advertisements posted at the local medical centre and at the University of Canterbury. Further, community talks and an in-house volunteer database were used for participant recruitment. The criteria for exclusion included reported

swallowing difficulties, neurological or muscular disease, gastrointestinal disease/reflux or drugs which might have an impact on swallowing. Ethical approval was obtained from the Human Ethics Committee of the University of Canterbury (HEC 2016/42). Prior to the start of data collection, participants received verbal and written information about the research and provided informed consent.

#### 9.2.1.2. *Instrumentation*

For data collection and for manometric biofeedback during training, the Given Imaging HRM ManoScan 360™ system (Model A120) with a ManoScan™ ESO catheter [EPS0042] at 2.75 mm diameter was used. The catheter housed 36 circumferential pressure sensors with 7.5 mm spacing between sensors. ManoView™ is the software intrinsic to the recording system and displays the data as either contour plots or line tracing.

#### 9.2.1.3. *Procedure*

Participants were seen for training one hour every day for two weeks (10 days) and for a follow-up session after a training break of two weeks to assess retention. Training duration and frequency were consistent with those reported in a previous study from this laboratory that evaluated pharyngeal pressure modulation (Lamvik et al., 2015). Baseline measures were collected at the beginning of the first session prior to initiation of training. Outcome measures were taken after both one and two weeks of practice (at the completion of the fifth and tenth session), as well as at follow-up.

At the start of the first session, participants were familiarised with HRM contour plots as biofeedback; for some subjects it was the first time to undergo HRM. Calibration was then routinely performed per standard operating instructions. For catheter placement, subjects were seated comfortably in a chair. No topical anaesthesia was applied to avoid the potential for altered swallowing function (Guiu Hernandez et al., 2017; Lamvik, 2016; Lester et al., 2013) and as there is evidence to suggest that topical anaesthesia does not improve comfort (Guiu Hernandez et al., 2017; Kwong, 2018). After application of lubricating gel on the catheter tip, the catheter was placed transnasally using a routine protocol (Knigge et al., 2014; Lamvik et al., 2015). Once sensor one was located just inside the naris and sensor 36 was in the cervical oesophagus, enabling evaluation of the upper aerodigestive tract in its entirety, the catheter was fixed with tape to the external nose. Participants were given two minutes to adjust to the catheter in situ before initiation of training. A shorter adjustment time than the commonly reported duration of five to ten minutes was selected due to the smaller catheter size (2.75 mm)

used in this study as compared to the commonly utilised 4.2 mm catheter in studies using pharyngeal HRM.

#### 9.2.1.4. *Baseline Measures*

For acquisition of baseline measures, participants were first asked to sit comfortably and quietly in a chair for two minutes ('I first need you to be as naturally as possible and sitting comfortably for two minutes. Please do not talk and only swallow when necessary'). The HRM monitor was turned away to avoid potential influence of biofeedback on performance. Baseline measures were acquired during this task to collect measures in a natural, non-manipulation condition. Next, the HRM monitor was turned such that the subjects were facing the monitor. Subjects were asked to increase UES resting pressure as much as possible for two minutes with the support of ongoing visual manometric biofeedback. Following a break of 30 s, subjects then attempted to decrease resting pressure for two minutes ('Make the colours as warm (or 'cold' for relaxation) as possible. Try to do this by specifically controlling the muscles at the entrance to the food tube rather than changing head or neck position or moving other muscles. Only swallow when necessary'). No counterbalancing of order between the pressure increase and decrease task was used as clinical experience suggests that muscle relaxation may be facilitated following muscle contraction. Baseline measures were identical to the outcome measures; they are detailed in section 9.2.1.6.

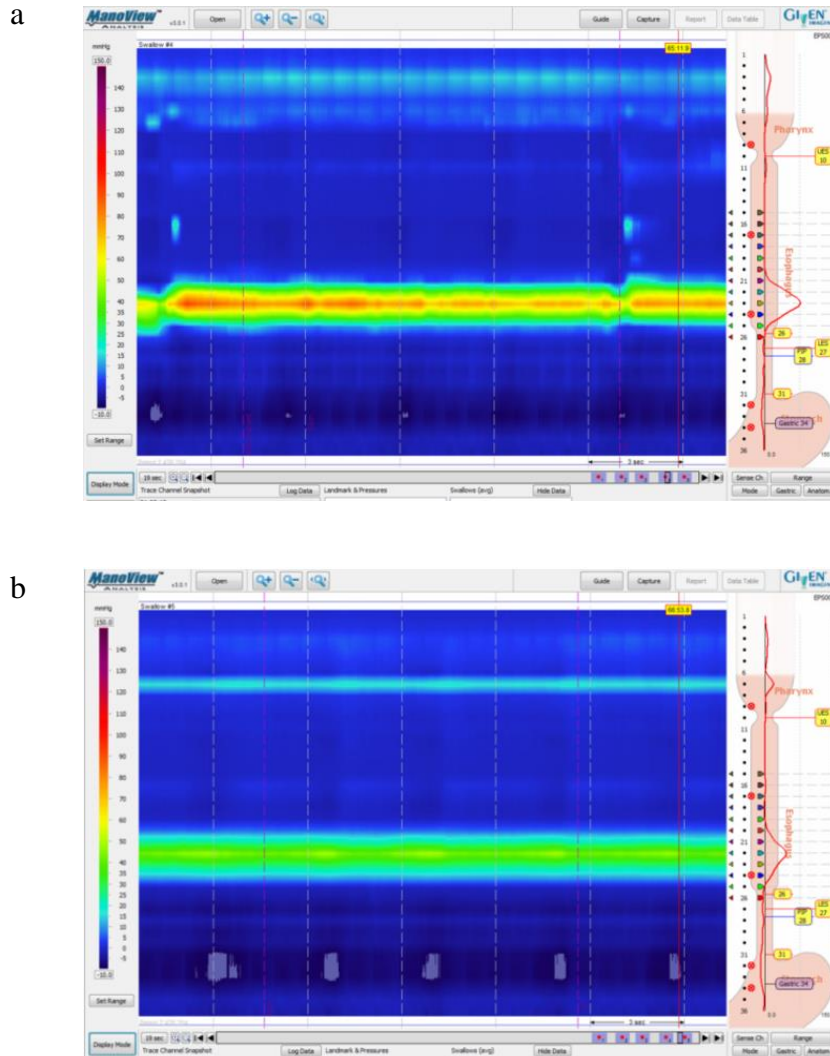
#### 9.2.1.5. *Training*

Participants were provided general instructions and a description of the goal of the training, namely, to modulate UES pressure at rest. No specific method was directly trained or instructed by the researcher; subjects were asked to self-explore how to manipulate pressure with support of the ongoing visual biofeedback (Nelson, 2007). Participants were seated upright in a chair facing the HRM monitor. The monitor was positioned such that participants could see the contour plots while keeping their head in a neutral position.

Subjects attempted to increase UES resting pressure for two minutes. Following a break of 30 s, subjects then attempted to decrease resting pressure for two minutes (Figure 28). This sequence was repeated eight times per session. The same verbal instruction as stated for the baseline measures (section 9.2.1.4) was given at the beginning of each training session and was repeated once in the middle of the session. A paper with the note 'as cold as possible' or 'as warm as possible' was placed in front of the HRM screen to remind the participants of the ongoing task. An alternate pressure increase and decrease protocol was selected as there is the



potential for different outcomes of the two tasks. Further, alternating tasks provided a contrast in extremes of behaviour; clinical experience suggests that this may support a participant's performance.



**Figure 28.** High-resolution manometry (HRM) biofeedback of upper oesophageal sphincter (UES) resting pressure during the pressure increase task (a), and the pressure decrease task (b).

Other than visual manometric biofeedback, verbal acknowledgement was controlled. This included ‘good try’ or ‘keep it up’ and was provided by the researcher during training breaks three times, evenly spread within each session. Additionally, verbal feedback about change in performance was provided at the beginning of the second training week; this potentially supported motivation and acknowledged commitment.

At the end of each session, participants were invited to descriptively write what they did during training to best achieve the task goal. This qualitative description was obtained to gain insight into the type of strategies applied by the subjects (Neergaard, Olesen, Andersen, & Sondergaard, 2009; Sandelowski, 2000). No structured questionnaire was used to avoid potential influence on participants' techniques. Open-ended questions were used as depicted in *Appendix D.1*.

#### 9.2.1.6. Outcome Measures

Outcome measures were collected at the completion of session 5 and session 10 and at the follow-up. Participants performed the same tasks as for assessment of baseline measures (Section 9.2.1.4). Baseline/outcome measures involved the following:

1. *UES resting pressure (mmHg)*: The mean UES pressure was extracted across 10 s based on the two middle sensors measuring UES pressures at rest (see section 9.2.1.7.1 for details). As the UES was at rest, UES sensors were defined as sensors located in the UES showing pressure recordings of  $\geq 5$  mmHg. The ManoScan<sup>TM</sup> system has an error of  $\pm 4$  mmHg for pressure larger than 50 mmHg (Given Imaging, 2016). Therefore, a 1 mmHg margin above the error threshold was selected ( $\geq 5$  mmHg) as a cut-off value to select UES sensors. If, during manipulation attempts, pressure recordings of  $\geq 5$  mmHg were found not only at the UES but also in the pharynx, UES sensors for analysis were those identified during the period of no manipulation. Measurements were based on the middle sensors rather than on all UES sensors to decrease the risk of including sensors with positive pressure recordings but located in the pharynx or oesophagus. The duration of 10 s rather than the recorded two minutes was chosen for measurement purpose to allow for exclusion of periods of non-task specific events such as swallowing or coughing. A period shorter than 10 s was considered inappropriate to reflect a volitionally controlled behaviour which requires control over time.
2. *The number of sensors recording UES resting pressure*: The cricopharyngeus is the primary muscular component of the UES. This baseline measure was evaluated to assess if modulated UES resting pressure was associated with a change in the number of sensors recording pressure at the UES. In other words, this measure was used to determine if the region of the UES expands or diminishes during behavioural pressure manipulation.
3. *The number of sensors recording pharyngeal pressure at rest*: The number of pharyngeal sensors recording  $\geq 5$  mmHg at rest was extracted to gain insight whether participants

achieved UES pressure manipulation in isolation of pharyngeal pressure alteration, as per instruction. No recorded pressure in the pharyngeal sensors would suggest that participants achieved discrete pressure manipulation at the UES. Pharyngeal sensors were defined as sensors located rostral to the uppermost UES sensor. As stated above, 5 mmHg was selected to account for the system's fidelity rate. In unclear situations, sensor selection was secondarily confirmed in the period of no manipulation.

#### 9.2.1.7. *Data Extraction*

After application of interpolated thermal compensation to account for a system-based measurement error (Lamvik et al., 2016), the recordings were coded to allow blinded data extraction and analysis. Due to methodological differences, blinding was not possible for the follow-up session.

The main investigator extracted data of all baseline and outcome sessions; a randomly selected 20% of these sessions were extracted on a second occasion at least one week apart for assessment of intra-rater reliability. Another randomly selected 20% of the data was extracted by a second rater for evaluation of inter-rater reliability. The rater received verbal and written explanation about methods of data extraction by the principal investigator. The main researcher had approximately one year of experience in HRM data extraction, the speech and language therapist involved for inter-rater reliability had about two months of practice.

Baseline and outcome measures were extracted using ManoView<sup>TM</sup>; this software incorporates a Smart Mouse<sup>TM</sup> feature for obtaining quantitative data. It can be used for data extraction in either of the two visualisation modes. In the contour plot, an area of interest can be selected with the computer mouse using a rectangular area tool. Within this area, Smart Mouse<sup>TM</sup> provides measurements such as the maximum pressure. In the line trace mode, the duration between two selected time-points can be extracted. All extracted data were entered into an Excel file. Notably, during the period of data collection, an increasing number of pharyngeal catheter sensors malfunctioned. Thus, the sensor number of faulty sensors was additionally extracted.

##### 9.2.1.7.1. *UES Resting Pressure/Number of Sensors Recording UES Resting Pressure*

Data extraction was performed in three primary steps including selection of the UES measurement period, UES sensor selection, extraction of UES pressure data. Regarding selection of the measurement period, data from the first 10 s of each trial were not included in the analysis to allow the participant time to focus attention on task performance. Thus, data

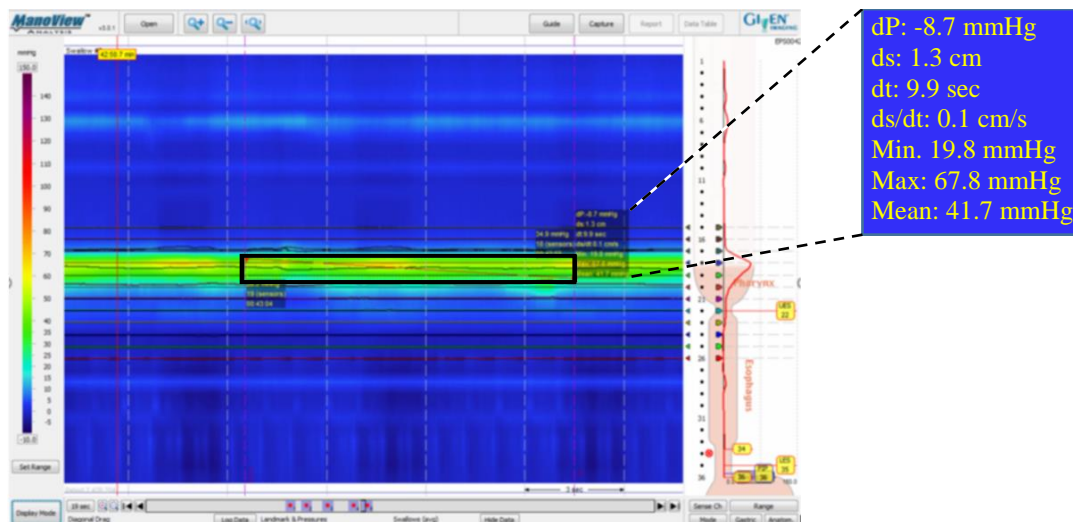
acquired between 10 and 20 s were marked in the line trace view for measurement. Exceptions were applied if:

- the subject swallowed during this period: to avoid confounding effects of swallow-related pressure changes, a measurement period post-swallow was used; the start of the measuring period was marked 10 s after the greatest swallowing-related drop in pressure (nadir) at the most rostral UES sensor showing a typical M-wave pressure pattern (Castell & Castell, 1993);
- non-task related behaviour other than swallowing such as coughing occurred during this period; the start of the measurement period was selected 2 s after the end of the event, as defined by the return of the pressure recordings to resting pressure levels;
- the measurement period from 10 to 20 s ended just prior to swallowing; as pre-swallowing-related pressure changes might confound measurement, a period starting 10 s post-swallow was marked.

For sensor selection, sensors located in the UES at rest were identified in the line trace view at the beginning of the measurement period. Out of the selected sensors (e.g. sensor number 19 - 22), the two middle sensors (e.g. sensor number 20 and 21) were determined. Exceptions were applied if:

- only one sensor showed pressure recordings of  $\geq 5$  mmHg at rest, thus, measurements were based on this single sensor;
- no sensor showed pressure values of  $\geq 5$  mmHg at rest, hence, the UES sensor recording the highest pressure at the start of the measurement period was selected;
- an uneven number of sensors recording resting pressure of  $\geq 5$  mmHg was identified, thus, pressure recordings of the most caudal pharyngeal sensor and the most rostral oesophageal sensor were considered to determine the two middle sensors. If the pharyngeal sensor showed higher pressure than the sensor in the oesophagus, the more rostral two of the three UES sensors were selected. If the sensor located in the oesophagus presented higher pressure than the one in the pharynx, the two distal sensors of the three UES sensors were selected;
- if pharyngeal and UES sensors could not be distinguished during the period of manipulation pharyngeal sensors were identified during the period of no manipulation.

For extraction of UES pressure data, the rectangular area incorporated in Smart Mouse™ feature was used to select UES sensors across the marked 10 s in the contour mode. The mean pressure within the selected area was displayed automatically (Figure 29).



**Figure 29.** The Smart Mouse™ feature captured the selected measurement period; quantitative data are listed at the corners of the box.

#### 9.2.1.7.2. *Number of Sensors Recording Pharyngeal Pressure at Rest*

Sensors in the pharynx with pressure recordings of  $\geq 5$  mmHg were identified in the line trace mode at the beginning of the measurement period. Malfunctioning pharyngeal sensors were considered for analysis; these sensors are reported in Appendix D.2 to avoid confounding effects on interpretation.

#### 9.2.1.8. *Data Analysis*

The analysis involved assessment of measurement reliability, evaluation of the potential for UES pressure modulation following training and without training, and evaluation of pharyngeal pressure to understand if pressure manipulation at the UES was achieved in isolation of pharyngeal pressure changes, as per instruction. Table 19 provides an overview of the analyses performed.

##### 9.2.1.8.1. *Reliability*

Reliability was evaluated using ICC for agreement of single measures. ICC estimates and their 95% confidence interval were calculated using R software (R Core Team, 2016). Intra-rater reliability was calculated based on a two-way mixed effects model [ICC(3,1)], inter-rater reliability on a two-way random effects model [ICC(2,1)] (Shrout & Fleiss, 1979). Separate reliability analyses were performed for each outcome measure. Results were interpreted using published criteria by Portney and Watkins (2009): poor reliability (ICC  $\leq 0.50$ ), moderate reliability (ICC 0.50 - 0.75), good reliability (ICC  $\geq 0.75$ ).

**Table 19.** Different aspects of data analysis

Aspect of data analysis		Methods
Reliability (section 9.2.1.8.1)		Intra- and inter-rater ICC for data extraction of UES resting pressure.
Quantitative Analysis (section 9.2.1.8.2)	Descriptive statistics	Mean, median, and interquartile range of UES resting pressure separated by task and session.  Difference in number of sensors located in the UES during manipulation as compared to no manipulation per participant and session.
	Performance with training	Differences in UES resting pressure for the outcome sessions compared to session 1: <i>Analysis 1</i> using manipulated resting pressure as dependent variable, <i>Analysis 2</i> using normalised resting pressure as dependent variable.
	Performance without training	Difference in UES resting pressure during manipulation compared to no manipulation at session 1.
	Pharyngeal pressure alterations	Number of sensors recording pharyngeal pressure during task performance per participant and session.
Qualitative Analysis (section 9.2.1.8.3)		Open-ended questions which strategy helped most per session/overall to achieve increased or decreased UES resting pressure.

*Note.* ICC = intraclass correlation coefficient, UES = upper oesophageal sphincter

#### 9.2.1.8.2. *Quantitative Analysis*

*Descriptive statistics:* Descriptive statistics included mean, median and interquartile range of UES resting pressure separated by task and session. Further, the difference of the number of sensors recording UES pressure during manipulation and during no manipulation was calculated per participant and session.

*Performance with training:* This analysis was performed to gain insight into the capacity of healthy subjects to behaviourally manipulate pressure given daily biofeedback training. To determine the effect of a one- and two-week training protocol on performance, outcome measures of the fifth and the tenth session were compared to baseline measures acquired at session 1. To reveal information about the potential for retention in performance, outcome measures from the follow-up were compared to baseline measures. Separate analyses were performed for the resting pressure increase and the pressure decrease task to ensure that the opposite directional effects required in the tasks did not obscure evidence of change in either direction. First, data were evaluated using scatter plots. For detection of potential outliers, box plots displaying data across participants separated by session were visually inspected. Q-Q-plots of the residuals and residuals versus fitted plots were additionally used to detect outliers if data analysis was performed using linear mixed effects models. Individual data points of interest were then reviewed to determine if the outlier was result of a measurement or typing error. If the latter was the case, the measurement of the specific observation was repeated, and the value replaced accordingly. If no evident error was detected, the outlier was included in analyses with no modification.

The relationship between task performance and training was evaluated conducting a linear mixed effects model analysis with lme4 package (Bates et al., 2015) in R software (R Core Team, 2016). Within-subject variability of non-manipulated UES resting pressure across sessions was expected as resting pressure is significantly influenced by factors such as a participant's emotional status (Jungheim et al., 2014b). However, it is unclear if the degree to which a subject can behaviourally modulate UES resting pressure is affected by the UES resting pressure during no manipulation at a specific session. Thus, two analyses were performed using different dependent variables. *Analysis 1* used the mean manipulated resting pressure as the dependent variable in the model. Data of the non-manipulation task were not included in analysis as no impact of the non-manipulated UES resting pressure on resting pressure during manipulation was assumed. The categorical session variable was entered as a

fixed effect with session 1 as the reference category. A by-subject random intercept was included to account for the repeated measures design. A  $p$ -value  $\leq .05$  was considered significant. *Analysis 2* assumed an impact of the non-manipulated UES resting pressure on resting pressure during manipulation. The non-manipulated mean resting pressure was subtracted in each baseline and outcome session from the manipulated mean resting pressure of the according session – the difference value was used as the dependent variable. This difference is referred to as 'normalised resting pressure'. The same fixed and random effects were used as for *Analysis 1*.

The assumptions for analysis were checked. Residual versus fitted plots were visually inspected for the selected model to detect any variance patterns of the residuals. Q-Q plots of the residuals and of the random effects were visually examined to identify any deviations from normality. If the assumptions of homoscedasticity and normality of the residuals and random effects were met, analyses using linear mixed models were continued. If the assumptions were violated, Friedman's non-parametric tests were performed to detect differences in outcome measures across time (Hollander, Wolfe, & Chicken, 2013). If results of a Friedman's test were significant, Wilcoxon signed-rank tests were conducted for post-hoc comparisons. To account for multiple comparisons of the Wilcoxon signed-rank tests,  $p$ -values were adjusted using a false discovery rate step-down procedure; an adjusted  $p$ -value  $\leq .05$  was considered significant.

*Performance without training:* To assess whether pressure modulation was achieved with no training, baseline measures (session 1) acquired during no manipulation and during manipulation were compared. For comparison, a dependent t-test was performed if the assumption for normality of the data was met. Assumptions of normality were checked as stated above. For non-normally distributed data, Wilcoxon signed-rank tests were used for analysis. A significant difference between manipulated and non-manipulated pressures would suggest a potential for manipulation without training.

*Pharyngeal pressure alterations:* To evaluate the effect of UES pressure modulation on pharyngeal pressure, the number of pharyngeal sensors recording pressure  $\geq 5$  mmHg during task performance per subject and session were reported.

#### 9.2.1.8.3. *Qualitative Analysis*

Participants' descriptions about strategies that helped most to achieve the goal were analysed using qualitative content analysis. Codes which were inductively derived from the data were



systematically applied for categorisation of the data (Pope, Ziebland, & Mays, 2000; Sandelowski, 2000).

### 9.2.2. Results

Six healthy female adults participated in this study; the age ranged from 22 to 48 years with a mean age of 30.6 years. The training protocol was completed by all subjects without adverse effects. Data collection was performed as planned, yet with some technical challenges related to faulty catheter sensors. Importantly, the catheter could be placed without any faulty sensors located in the UES. However, some malfunctioning sensors were located in the pharynx; the number of faulty pharyngeal sensors from which pressure recordings were included into analysis are depicted in *Appendix D.2*. The instruction for the first participant during the first training week did not specify that pressure manipulation should be achieved without altering head and neck position or contracting other muscles than the UES sphincter muscles. Thus, the data of the first participant during the manipulation tasks during the first week were excluded from analysis. The instruction was complemented with this information for the second training week of the first participant and for all following subjects.

#### 9.2.2.1. Reliability

The ICCs indicate good intra- and inter-rater reliability of UES resting pressure during the pressure manipulation tasks. Table 20 depicts the reliability estimates.

**Table 20.** Reliability of UES resting pressure

	<b>Intra-rater ICC (95% CI)</b>	<b>Inter-rater ICC (95% CI)</b>
Mean UES resting pressure (mmHg)	.98 (.96, .99)	.89 (.77, .95)

*Note.* ICC = intraclass correlation coefficient, CI = confidence interval

#### 9.2.2.2. Quantitative Analysis

*Descriptive statistics:* Mean, median and interquartile range of the mean UES resting pressure during the baseline/outcome tasks across participants per session are reported in Table 21. Table 22 depicts the difference in number of sensors located in the UES during manipulation as compared to no manipulation. There was limited evidence that attempts to achieve higher UES resting pressure were associated with pressure increases across a broader anatomical

region. During attempts to decrease pressure, fewer sensors recorded pressure at the UES compared to during no manipulation in some participants.

**Table 21.** Average UES resting pressure: Mean, median (interquartile range)

Session	Non-manipulation task	Pressure increase task	Pressure decrease task
1	38.62 mmHg, 31.75 mmHg (23.90)	58.60 mmHg, 63.10 mmHg (5.10)	24.12 mmHg, 25.10 mmHg (16.10)
5	31.72 mmHg, 31.50 mmHg (8.85)	108.66 mmHg, 106.50 mmHg (6.20)	29.28 mmHg, 27.40 mmHg (19.00)
10	32.95 mmHg, 31.55 mmHg (14.35)	86.13 mmHg, 89.50 mmHg (33.38)	24.05 mmHg, 22.70 mmHg (12.10)
Post-training	23.88 mmHg, 23.75 mmHg (6.78)	91.18 mmHg, 86.85 mmHg (97.25)	24.48 mmHg, 27.40 mmHg (6.43)

Note. UES = upper oesophageal sphincter

**Table 22.** Differences in the number of UES sensors during the pressure increase/pressure decrease task as compared to the non-manipulation task

Participant	Session 1	Session 5	Session 10	Post-training
1	NA	0 / -1	0 / 0	+1 / +1
2	0 / 0	+1 / 0	+1 / +1	-1 / 0
3	0 / -1	0 / 0	+1 / 0	-1 / 0
4	0 / -6	-4 / -6	+3 / -6	+5 / -4
5	0 / -1	0 / 0	+0 / 0	0 / 0
6	+1 / -2	+1 / -2	+1 / 0	+1 / +1

Note. UES = upper oesophageal sphincter, NA = not applicable because these data were excluded from analysis

*Perforamnce with training:* The assumptions for analysis using linear mixed effects models were satisfied for both pressure manipulation tasks. Based on *Analysis 1*, the estimated mean UES resting pressure across participants during the pressure increase task at session 1 was 51.68 mmHg (95% CI [20.19, 86.13]); for the pressure decrease task, it was 24.40 mmHg (95% CI [13.19, 35.55]). For the pressure increase task, a training effect was found after one week of practice. There was no training effect for the pressure decrease task at any of the analysed time-points. Table 23 depicts the training effect on task performance.

**Table 23.** Estimated differences in mean UES resting pressure during manipulation at the outcome sessions compared to session 1

Session	Pressure increase task	Pressure decrease task
5	+50.06 mmHg (95% CI [10.82,88.14], $p = .02^*$ )	+5.16 mmHg (95% CI [-4.03, 14.70], $p = .30$ )
10	+34.45 mmHg (95% CI [-0.92,68.94], $p = .09$ )	-0.35 mmHg (95% CI [-9.43, 8.70], $p = .94$ )
Post-training	+39.50 mmHg (95% CI [4.46, 76.41], $p = .053$ )	+0.08 mmHg (95% CI [-9.04, 8.77], $p = .99$ )

Note. UES = upper oesophageal sphincter, CI = confidence interval, \*significant at  $p \leq .05$

Based on *Analysis 2*, the estimated normalised mean UES resting during the pressure increase task across participants at session 1 was 15.65 mmHg (95% CI [-16.52, 46.45]), during the pressure decrease task it was -15.50 mmHg (95% CI [-27.87, -0.65]). As depicted in Table 24, a training effect was revealed after one week and at the post-training session for performance during the pressure increase task. For the pressure decrease task, a significant increase in pressure was found at session 1 and at the follow-up. UES resting pressure during the non-manipulation task is illustrated in Table 25. At session 1, the estimated mean UES resting pressure during no manipulation across participants was 38.62 mmHg (95% CI [28.99, 48.42]); notably, significantly lower pressure was found at the follow-up compared to session 1. This pressure drop amplifies the training effect for the pressure increase task but reduces the effect for the decrease task.

**Table 24.** Estimated differences of the normalised mean UES resting pressure for the outcome sessions compared to session 1

Session	Pressure increase task	Pressure decrease task
5	+59.24 mmHg (95% CI [18.04, 100.64], $p = .02^*$ )	+14.34 mmHg (95% CI [4.02, 24.28], $p = .02^*$ )
10	+37.53 mmHg (95% CI [-3.57,78.45], $p = .10$ )	+6.60 mmHg (95% CI [-3.79, 16.29], $p = .22$ )
Post-training	+51.65 mmHg (95% CI [8.59, 95.23], $p = .03^*$ )	+16.10 mmHg (95% CI [6.10, 25.81], $p = .01^*$ )

Note. UES = upper oesophageal sphincter, CI = confidence interval, \*significant at  $p \leq .05$

**Table 25.** Estimated differences in mean UES resting pressure during no manipulation for the outcome sessions compared to session 1

Session	No manipulation task
5	-6.90 mmHg (95% CI [-20.29, 6.22], $p = .33$ )
10	-5.67 mmHg (95% CI [-19.47, 6.39], $p = .42$ )
Post-training	-14.73 mmHg (95% CI [-28.04, -1.26], $p = .05^*$ )

Note. UES = upper oesophageal sphincter, CI = confidence interval, \*significant at  $p \leq .05$

*Performance without training:* Evaluation of performance without training revealed no evidence of an increase of the mean UES resting pressure during the pressure increase task as compared to the non-manipulation task at session 1. For the pressure decrease task, there was no evidence of a mean pressure decrease from no manipulation. Table 26 illustrates the potential for pressure manipulation at session 1.

**Table 26.** Estimated differences in UES resting pressure for both pressure manipulation tasks as compared to no manipulation at session 1

Session	Pressure increase task	Pressure decrease task
1	+18.32 mmHg (95% CI [-0.54, 37.18], $p = .054$ )	-16.16 mmHg (95% CI [-47.31, 14.99], $p = .22$ )

Note. UES = upper oesophageal sphincter, CI = confidence interval

*Pharyngeal pressure alterations:* During the non-manipulation task and the pressure decrease task, none of the participants showed pharyngeal sensors with recording pressure  $\geq 5$  mmHg at any of the analysed sessions. As reported in Table 27, data of individual participants for the pressure increase task indicate that four of six participants showed no pharyngeal pressure recordings at any of the analysed sessions.

**Table 27.** Number of pharyngeal sensors with pressure  $\geq 5$  mmHg during the pressure increase task

Participant	Session 1	Session 5	Session 10	Post-training
1	NA	0	0	0
2	0	0	0	0
3	0	1	10	12
4	1	0	0	2
5	0	0	0	0
6	0	0	0	0

NA = not applicable because these data were excluded from analysis

### 9.2.2.3. *Qualitative Analysis*

The following categories summarise the self-identified techniques which were helpful to achieve an increase in UES resting pressure according to the participant's written descriptions:

- visualisation (e.g. to visualise contracted UES muscles),
- imagination (e.g. to imagine being an opera singer),
- relaxation (e.g. to relax the tongue),
- focus on breathing (e.g. to exhale while contracting the UES),
- focus on heartbeat (e.g. to change the heartbeat),
- focus on biofeedback,
- swallowing (e.g. to start task performance with a swallow),
- muscle contraction at the level of the UES (e.g. to contract the muscles around the catheter),
- contraction of muscles other than the UES muscles (e.g. to push the tongue back),
- and other techniques (e.g. to almost gag).

As the most helpful strategy overall, focusing on breathing was mentioned by three participants and to start task performance with a swallow was mentioned by two participants.

For the pressure decrease task, the following categories summarise the participant's feedback:

- visualisation (e.g. to visualise a relaxed UES),
- imagination (e.g. to imagine eating a favourite food),
- relaxation (e.g. to meditate),
- focus on breathing (e.g. to breathe shallowly),

- focus on heartbeat (e.g. to listen to heartbeat),
- contraction of muscles (e.g. to move the tongue),
- focus on biofeedback,
- and others (e.g. to hold an air bubble in the throat).

As the most helpful techniques overall, relaxation and breathing techniques were mentioned by most of the participants.

### **9.3. Exploratory Study 2: Behavioural Pressure Manipulation during Swallowing**

#### **9.3.1. *Materials and Methods***

##### *9.3.1.1. Participants*

Six participants were recruited for this study; these subjects were not the same that participated in Exploratory Study 1. The criteria for exclusion were the same than for Study 1. Ethical approval was obtained as stated previously.

##### *9.3.1.2. Instrumentation*

The Given Imaging HRM ManoScan 360™ system (Model A120) with a ManoScan™ ESO catheter [EPS0042] (2.75 mm diameter) was used for data collection and for visual biofeedback during training.

##### *9.3.1.3. Procedure*

Participants attended daily training for two weeks and were seen for a follow-up session after a break of two weeks. At the beginning of the first session, baseline measures were collected; outcome measures were taken after one and after two weeks of training and at the follow-up. According to the procedure stated for Study 1, participants were familiarised with HRM as biofeedback; for some of the subjects this was the first exposure to HRM. Then, system calibration was performed, and the catheter was placed.

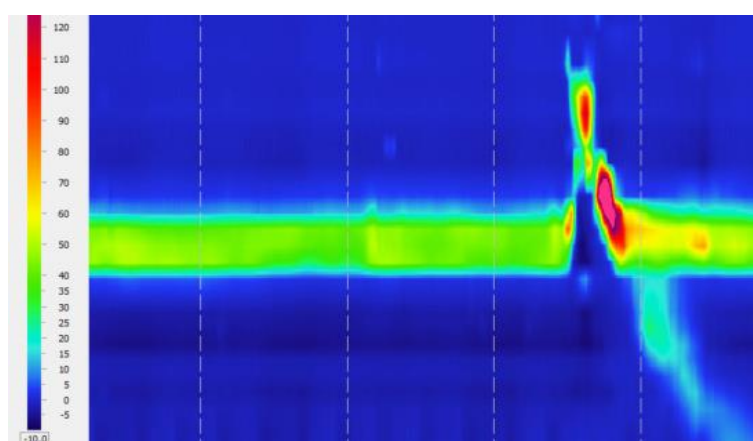
##### *9.3.1.4. Baseline Measures*

For acquisition of baseline measures, participants were asked to perform five natural saliva swallows followed by five swallows of 10 mL water from a 20 mL plastic cup; no biofeedback was provided ('Once I give the instruction, please swallow your saliva ('or water') as naturally as possible whenever you are ready'). A period of at least 30 s between swallows was selected to allow participants time to accrue saliva and to allow UES pressure to reach natural resting

pressure post-swallow prior to the subsequent swallow. Next, the subjects were asked to increase the duration of intra-swallow relaxation during five saliva and five water swallows with visual feedback provided (‘While swallowing saliva, try to get the period of dark blue as long as possible. Try to do this by specifically controlling the muscles at the entrance to the food tube rather than by changing head or neck position or moving other muscles’). Baseline and outcome measures were collected for saliva and water swallows to determine if performance for saliva swallowing during training generalised to bolus swallowing. For both tasks, saliva swallows were evaluated first followed by water swallows. The main outcome measure, the trained task without bolus swallowing, was evaluated first to avoid a potential impact of bolus swallowing on the main outcome measure. Baseline and outcome measures are identical; they are reported in section 9.3.1.6.

#### 9.3.1.5. Training

As stated for Study 1, no specific method was instructed. Participants were asked to self-explore how to prolong the duration of UES opening during swallowing by *direct* pressure manipulation of the UES rather than by biomechanical alteration of the swallowing response. The identical verbal instruction as for the baseline measures (9.3.1.4) was provided at the beginning and in the middle of each session (Figure 30). No specific method was directly trained or instructed by the researcher. In each two-minute block, participants swallowed saliva four times, approximately once every 30 s. After each block, participants had a break of 45 s. In total, 16 two-minute blocks or a total of 64 training swallows were performed per session.



**Figure 30.** High-resolution manometry (HRM) biofeedback of the upper oesophageal sphincter (UES) opening duration during the manipulation task.

As stated for Study 1, verbal feedback about task maintenance and about change in performance after one week of training compared to no training was provided. Participants were invited to write down what they did to best achieve the task goal at the conclusion of each session. *Appendix D.1* illustrates the questions that were used.

#### 9.3.1.6. *Outcome Measures*

Outcome measures were collected at the end of session 5 and 10 and at the post-training session. The same tasks were performed by the participants as for evaluation of baseline measures. Baseline/outcome measures were the following:

1. *Duration of pressure related UES opening (s)*: Sensors located in the UES during swallowing were identified based on their pressure patterns; the most rostral sensor showing a pressure pattern similar to an ‘M-wave’ (Castell & Castell, 1993) was defined as the upper most UES sensor. The last UES sensor was defined as the middle sensor of all sensors recording pressure at the UES at rest, as described in Study 1. This sensor, rather than a more caudal sensor, was chosen to minimise the risk of including oesophageal pressure data into analysis. For measurement, the one UES sensor which recorded the most negative intra-swallow pressure (nadir pressure) was selected. The starting point of the measurement period was defined by a pressure drop of 10% below UES resting pressure; the end was determined when the same pressure was reached again post-nadir (S. Meyer et al., 2012).
2. *Pharyngeal maximum pressure (mmHg)*: One amplitude and one temporal pharyngeal measure were extracted to capture potential concurrent pressure changes in the pharynx during pressure modulation at the UES. Further, pharyngeal measures were assessed over the course of the training period to evaluate whether pharyngeal pressure changed as an effect of pressure modulation at the UES. The maximum pressure was calculated across a selected area; the area was defined vertically by the most rostral and the most distal pharyngeal sensor and horizontally by the start and end of the pressure recordings of these two sensors. The maximum, rather than the mean, pressure was extracted to detect any pressure alterations, including brief pressure peaks that may support participants in achieving the task goal. The most rostral pharyngeal sensor was defined as the one next to the most caudal sensor located in the velopharynx; sensors in the velopharynx were identified based on the pressure recordings which started slightly earlier than those of the pharyngeal sensors. The most caudal pharyngeal sensor was defined as the one adjacent to



the most rostral UES sensor. Sensors at the border of pharynx and UES tend to move vertically during swallowing; the most caudal pharyngeal sensor was the one located in pharynx at all time points during swallowing.

3. *Pharyngeal normalised time (ms/cm)*: The pharyngeal normalised time was calculated as the time between the peak pressure of the most rostral pharyngeal sensor to the peak pressure of the most distal pharyngeal sensor divided by the distance of these two sensors (7.5 mm). The pharyngeal normalised time rather than the more commonly reported velocity (cm/ms) was extracted for a mathematical reason. Velocity is calculated by dividing a distance measure by a duration measure. During performance of the training task, simultaneous pressure peaks in the pharynx were found in some participants. In these cases, the distance measure would be divided by the duration of zero, which is mathematically impossible.

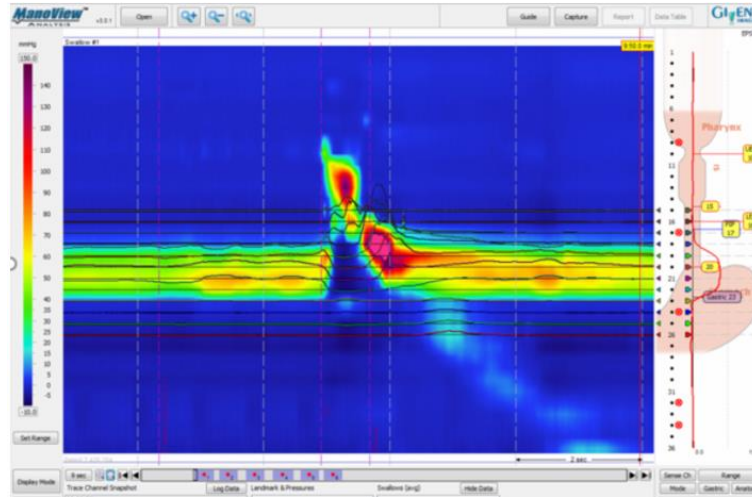
#### 9.3.1.7. *Data Extraction*

Interpolated thermal compensation was applied and the recordings were encoded. As stated previously, the main researcher extracted data of all baseline and outcome sessions and additionally a randomly selected 20% of these sessions for evaluation of intra-rater reliability. A second rater with about two years of experience in HRM data extraction, extracted data of another randomly selected 20% of the data for assessment of inter-rater reliability.

Baseline and outcome measures were extracted using ManoView™ and external software MATLAB (MATLAB R2014a, The MathWorks Inc., Natick, MA, 2014). The beginning of each swallow considered for analysis was annotated in the line trace mode in ManoView™. This enabled data export of these swallows via text files into MATLAB later in the process of data extraction. Prior to data extraction, malfunctioning sensors were identified, and the sensor numbers noted.

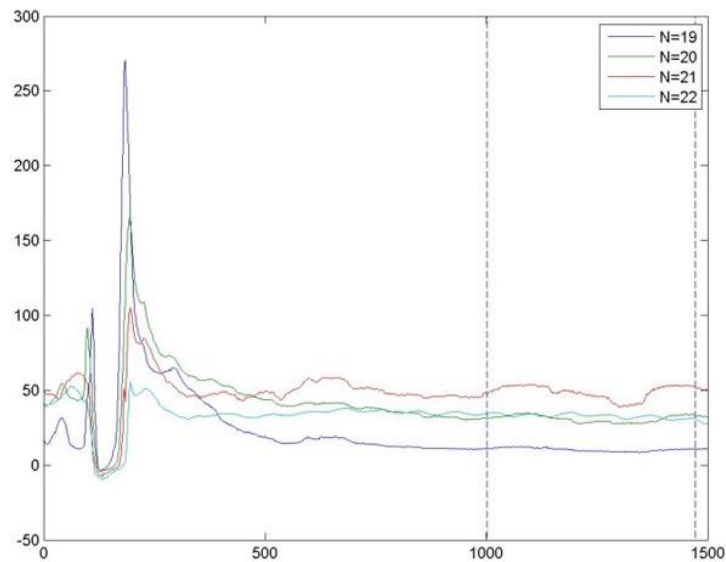
##### 9.3.1.7.1. *Duration of Pressure Related UES Opening*

*Data extraction using ManoView™*: For the UES opening duration, data extraction in ManoView™ involved selection of sensors at the UES at rest and during swallowing. UES sensors at rest were visually identified post-swallow using the line trace mode. Sensors were included if the recorded pressure  $\geq 5$  mmHg at rest. Malfunctioning sensors were not considered to ensure that findings were not confounded by interpolated data. Sensors at the UES during swallowing were identified, as stated earlier (section 9.3.1.4). For sensor selection, line traces and contour plots were super-imposed (Figure 31).



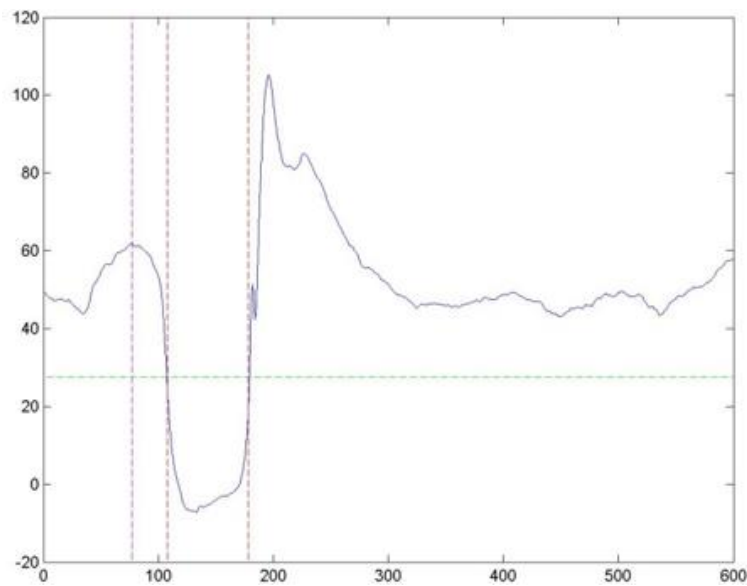
**Figure 31.** High-resolution manometry (HRM) line trace and contour mode superimposed.

*Data extraction using MATLAB:* Data extraction using MATLAB software involved selection of the measurement period for UES resting pressure, calculation of the mean UES resting pressure, and calculation of the duration of pressure related UES opening. For selection of the measurement period for UES resting pressure, for each swallow, the previously selected UES sensors measuring resting pressure post-swallow were automatically imported into MATLAB. Pressure recordings of the associated sensors were displayed as line traces in a window generated by the software. The window displayed 15 s (1500 samples) of data, depicting the annotated swallow and the post-swallow period. The researcher determined the start- and end-point of a period of stable UES resting pressure post-swallow by two manual clicks on the line traces. Where the clicks were applied, two vertical lines were automatically generated (Figure 32). In the literature, an average duration of 10 s post-swallow has been reported for UES resting pressure to resume pre-swallow resting pressure values (Jungheim et al., 2016). Thus, to avoid inclusion of elevated UES resting pressure post-swallow, the start of the measurement period was set at 10 s after the swallow or later. The measurement duration was not specified; the longest possible period of stable pressure was selected. The average UES resting pressure across all displayed sensors within the tagged period was automatically calculated.



**Figure 32.** MATLAB: The coloured line traces represent the sensors at the upper oesophageal sphincter (UES) recording resting pressure. The sensor numbers are displayed in a box in the upper right corner of the window. The two vertical dotted lines show the manually marked period of stable UES resting pressure post-swallow.

For calculation of the duration of pressure related UES opening, the sensors recording UES pressure during swallowing were automatically derived from the Excel file for each swallow. The sensor recording the most negative pressure intra-swallow was automatically identified. Six seconds of pressure recording for this sensor was displayed in a window. Additionally, a horizontal line corresponding to the pressure value 10% below the previously calculated mean UES resting pressure was generated. This line served as a visual guideline for the researcher. The researcher manually placed a tag on the displayed UES sensor just before a drop of pressure indicated the start of UES opening. This tag marked the point in the data when a pressure drop by 10% from the mean UES resting pressure was identified. Next, two vertical lines were generated. One line marked the time point of a pressure drop by 10% from the mean UES resting pressure, the other one indicated when the same pressure was reached again post-nadir (Figure 33). The duration between these two time-points was automatically calculated.



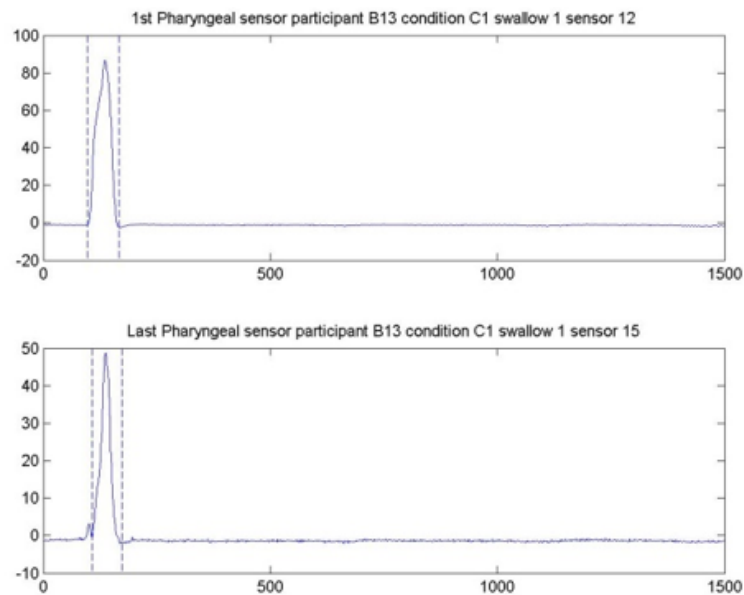
**Figure 33. MATLAB:** The grey continuous line shows the pressure recording of the selected sensor at the upper oesophageal sphincter (UES). The dashed green line indicates the pressure value 10% below mean UES resting pressure. The purple line shows from where a pressure drop by 10% of mean UES resting pressure will be identified. The two dashed red lines show the start and end of the UES opening period.

#### 9.3.1.7.2. *Pharyngeal Maximum Pressure and Pharyngeal Normalised Time*

*Data extraction using ManoView™:* For the pharyngeal measures, data extraction in ManoView™ included selection of the pharyngeal sensors. Pharyngeal sensors were identified as described earlier (section 9.3.1.4) by visual inspection of the line traces. It was confirmed that the first and last pharyngeal sensor was properly working, as these sensors were used to define the measurement area. Pharyngeal sensors other than the first and last one were considered for analysis even if malfunctioning, as it was expected that interpolated data would have smaller confounding effects on the results than missing data.

*Data extraction using MATLAB:* Data extraction using MATLAB involved selection of the measurement period and calculation of the pharyngeal measures. The selected pharyngeal sensors were automatically imported for each swallow from the Excel file. For the most rostral and most caudal sensor, pressure recordings of 15 s were automatically displayed as line traces in two individual windows. For each line trace, a manual click was applied by the researcher at the point of pressure rise from baseline and where baseline pressure was reached again (Figure 34). Baseline pressure was defined as the continuous pressure recording pre-swallow. The pharyngeal measures were automatically calculated within an area of pressure recordings. The area was defined on the vertical axis, by the most rostral and most caudal pharyngeal

sensor. On the horizontal axis, the area was defined by the four cursors marking the start and end of the pressure recordings of these two sensors.



**Figure 34.** MATLAB: Pressure recordings of the most rostral and most caudal pharyngeal sensor are depicted. The dashed lines show the manually selected start- and end points of the pharyngeal pressure recordings during swallowing.

#### 9.3.1.8. *Data Analysis*

Data analysis included assessment of measurement reliability, evaluation of the potential for prolongation of UES opening following training and without training, and assessment of pharyngeal pressure patterns. The different analyses are depicted in Table 28; detailed information is provided subsequently.

##### 9.3.1.8.1. *Reliability*

Reliability was evaluated using the ICC, as stated for Study 1. Saliva and water swallows were analysed together. Two ICCs were calculated for both intra- and inter-rater reliability. For one calculation, the entire process of data extraction involving the use of ManoView™ and MATLAB was considered. For the other calculation, only data extraction using MATLAB was included. The two reliability coefficients were calculated to understand the influence of sensor selection (ManoView™) and measurement (MATLAB) on reliability.

**Table 28.** Different aspects of data analysis

Aspect of data analysis		Methods
Reliability (section 9.3.1.8.1)		Separate ICCs for data extraction of UES opening duration, pharyngeal maximum pressure, and pharyngeal normalised time.
Quantitative Analysis (section 9.3.1.8.2)	Descriptive statistics	Mean, median, and interquartile range of UES opening duration, pharyngeal maximum pressure, and pharyngeal normalised time for saliva and water swallows separated per task.
	Performance with training	Differences in UES opening duration for the outcome sessions compared to session 1.
	Performance without training	Difference in UES opening duration during manipulation compared to no manipulation at session 1.
	Pharyngeal pressure alterations	Differences in pharyngeal maximum pressure and pharyngeal normalised time for the outcome sessions compared to session 1; differences during manipulation compared to no manipulation at session 1.
Qualitative Analysis (section 9.3.1.8.3)		Open-ended questions regarding which strategy helped most per session/overall to achieve prolonged UES opening duration.

*Note.* ICC = intraclass correlation coefficient, UES = upper oesophageal sphincter

#### 9.3.1.8.2. *Quantitative Analysis*

*Descriptive statistics:* Descriptive statistics included mean, median and interquartile range for UES opening duration and the pharyngeal measures separated by task and session.

*Performance with training:* For evaluation of performance with training, outcome measures of session 5 and 10 and the follow-up were compared to baseline measures. Separate analyses were completed for saliva and water swallows as the presence of a bolus may influence UES opening. Analysis was performed as stated for study 1 (section 9.2.1.8.2), including plotting of data, identification of outliers, model selection for linear mixed effects analysis, and assumption checking. Session was entered as a fixed effect into the model and a by-subject random intercept was included. As participants performed five swallows per task, the inclusion of the by-subject random slope for the effect of session was tested by deleting the by-subject random slope from the full model that is the model including the by-subject random slope. The minimal adequate model was found by comparing the reduced model with the full model using a likelihood ratio test. If the assumptions were met, analyses using linear mixed models were continued; otherwise, Friedman's non-parametric tests were performed. Non-parametric analyses were based on average values of the five swallows per participant and per outcome task. Wilcoxon signed-rank tests were conducted for post-hoc comparisons if results of a Friedman's test were significant.

*Performance without training:* To evaluate the performance without training, baseline measures acquired during no manipulation and during manipulation were compared. The comparison was performed using linear mixed effects model rather than a t-test as in Study 1 to include all individual values of the five swallows per participant and task without averaging them. If the assumptions of normality were not met, the Wilcoxon signed-rank test was performed according to Study 1.

*Pharyngeal pressure alterations:* To detect potential pharyngeal pressure alterations, pharyngeal measures acquired during manipulation at the outcome sessions were compared to baseline measures at session 1 using linear mixed effects models if the assumptions of normality and homoscedasticity of the residuals were met. Otherwise, non-parametric statistics were performed as for the main outcome measure.

#### 9.3.1.8.3. *Qualitative Analysis*

Qualitative content analysis was used to analyse the participants' descriptions of their strategies to best achieve the task goal.

### 9.3.2. Results

Six healthy females with an age range of 23 to 68 years (mean age of 36 years) participated in this study. The training protocol was completed by all subjects without adverse events. The number of malfunctioning pharyngeal sensors that were considered for analysis are depicted in *Appendix D.2*. One participant was ill at the tenth session, hence, the session had to be postponed by three days. For another subject, the follow-up was preponed by three days due to participant availability.

#### 9.3.2.1. Reliability

Table 29 presents the reliability findings for the outcome measures. For the entire process of data extraction, good intra-rater and moderate inter-rater reliability were found for UES opening duration; findings indicated moderate intra-rater and good inter-rater reliability for pharyngeal maximum pressure and pharyngeal normalised time. For data extraction excluding sensor selection, intra- and inter-rater reliability was good for UES opening duration; moderate intra-rater and good inter-rater reliability were found for pharyngeal normalised time. No reliability was assessed for pharyngeal maximum pressure for MATLAB specific data extraction, as no manual measurements were required in MATLAB.

**Table 29.** Reliability of UES opening duration and pharyngeal measures during saliva and water swallows

Measure	Inter-rater ICC (95% CI) for data extraction: ManoView™ and MATLAB	Inter-rater ICC (95% CI) for data extraction: MATLAB	Intra-rater ICC (95% CI) for data extraction: ManoView™ and MATLAB	Intra-rater ICC (95% CI) for data extraction: MATLAB
Duration of pressure related UES opening (s)	.68 (.59, .76)	.81 (.75, .86)	.84 (.78, .88)	.87 (.83, .91)
Pharyngeal maximum pressure (mmHg)	.98 (.98, .99)	NA	.57 (.43, .68)	NA
Pharyngeal normalised time (ms/cm)	.87 (.76, .93)	.96 (.93, .97)	.70 (.59, .79)	.69 (.60, .77)

*Note.* UES = upper oesophageal sphincter, ICC = intraclass correlation coefficient, CI = confidence interval, NA = not applicable because a manual intervention was not required



### 9.3.2.2. Quantitative Analysis

*Descriptive statistics:* The mean, median, and interquartile range of the duration of UES opening across subjects per session are reported in Table 30; for pharyngeal maximum pressure in Table 31, and for pharyngeal normalised time in Table 32. The statistics are based on mean values of the five swallows performed per task.

*Performance with training:* The assumptions for linear mixed effects analysis were not met for saliva and water swallows. Results of the Friedman's test indicated that the UES opening duration of saliva swallows during manipulation changed significantly across time ( $\chi^2(3) = 8.6$ ,  $p = .04^*$ ). Post-hoc analysis revealed that there was no significant difference in manipulated UES opening duration at any of the analysed time-points compared to session 1. For water swallows, there was no significant change in manipulated UES opening duration across time ( $\chi^2(3) = 6.8$ ,  $p = .08$ ).

*Performance without training:* Non-parametric analysis of performance without training revealed that UES opening duration of saliva ( $p = 0.04^*$ ) and of water swallows ( $p = .03^*$ ) was longer during manipulation than during no manipulation at session 1. For saliva swallows, the median UES opening duration (based on the mean duration of five swallows) was 0.67 s during manipulation, and 0.51 s during no manipulation. For water swallows, the median UES opening duration during manipulation was 0.87 s and 0.74 s during no manipulation.

**Table 30.** Duration of pressure related UES opening: Mean, median (interquartile range) across participants

Session	Non-manipulation task	Manipulation task
1	Saliva: 0.52 s, 0.51 s (0.13)	Saliva: 0.78 s, 0.67 s (0.43)
	Water: 0.72 s, 0.74 s (0.09)	Water: 0.88 s, 0.87 s (0.08)
5	Saliva: 0.45 s, 0.44 s (0.07)	Saliva: 0.52 s, 0.47 s (0.06)
	Water: 0.54 s, 0.54 s (0.09)	Water: 0.73 s, 0.69 s (0.18)
10	Saliva: 0.46 s, 0.44 s (0.15)	Saliva: 0.48 s, 0.43 s (0.26)
	Water: 0.64 s, 0.59 s (0.12)	Water: 0.75 s, 0.74 s (0.13)
Post-training	Saliva: 0.52 s, 0.48 s (0.14)	Saliva: 0.71 s, 0.64 s (0.14)
	Water: 0.60 s, 0.62 s (0.09)	Water: 0.75 s, 0.78 s (0.14)

Note. UES, upper oesophageal sphincter

**Table 31.** Pharyngeal maximum pressure: Mean, median (interquartile range) across participants

Session	Non-manipulation task	Manipulation task
1	<i>Saliva:</i> 115.13 mmHg, 113.09 mmHg (24.26)  <i>Water:</i> 111.63 mmHg, 109.82 mmHg (25.07)	<i>Saliva:</i> 115.16 mmHg, 109.50 mmHg (22.11)  <i>Water:</i> 114.72 mmHg, 116.92 mmHg (5.03)
5	<i>Saliva:</i> 100.35 mmHg, 97.55 mmHg (18.75)  <i>Water:</i> 100.87 mmHg, 104.56 mmHg (18.48)	<i>Saliva:</i> 112.38 mmHg, 115.71 mmHg (10.70)  <i>Water:</i> 107.60 mmHg, 109.17 mmHg (29.43)
10	<i>Saliva:</i> 117.40 mmHg, 114.34 mmHg (9.55)  <i>Water:</i> 113.68 mmHg, 114.87 mmHg (8.04)	<i>Saliva:</i> 124.27 mmHg, 124.67 mmHg (18.23)  <i>Water:</i> 113.63 mmHg, 114.29 mmHg (25.69)
Post-training	<i>Saliva:</i> 115.77 mmHg, 111.98 mmHg (19.34)  <i>Water:</i> 100.50 mmHg, 97.04 mmHg (13.50)	<i>Saliva:</i> 111.62 mmHg, 115.32 mmHg (9.64)  <i>Water:</i> 98.43 mmHg, 94.25 mmHg (20.03)

**Table 32.** Pharyngeal normalised time: Mean, median (interquartile range) across participants

Session	Non-manipulation task	Manipulation task
1	<i>Saliva:</i> 29.61 ms/cm, 30.18 ms/cm (24.48)  <i>Water:</i> 52.10 ms/cm, 61.67 ms/cm (19.57)	<i>Saliva:</i> 44.92 ms/cm, 32.09 ms/cm (32.49)  <i>Water:</i> 50.64 ms/cm, 57.56 ms/cm (26.38)
5	<i>Saliva:</i> 29.22 ms/cm, 31.73 ms/cm (55.43)  <i>Water:</i> 42.61 ms/cm, 39.40 ms/cm (39.53)	<i>Saliva:</i> 27.21 ms/cm, 32.67 ms/cm (47.83)  <i>Water:</i> 37.78 ms/cm, 41.56 ms/cm (37.94)
10	<i>Saliva:</i> 24.93 ms/cm, 22.00 ms/cm (18.00)  <i>Water:</i> 24.93 ms/cm, 20.00 ms/cm (16.67)	<i>Saliva:</i> 32.50 ms/cm, 28.82 ms/cm (16.36)  <i>Water:</i> 27.51 ms/cm, 27.2 ms/cm (17.43)
Post-training	<i>Saliva:</i> 20.01 ms/cm, 11.33 (14.50)  <i>Water:</i> 26.59, ms/cm, 23.67 ms/cm (11.00)	<i>Saliva:</i> 18.72 ms/cm, 19.44 ms/cm (21.28)  <i>Water:</i> 21.16 ms/cm, 19.00 ms/cm (6.67)

*Pharyngeal pressure alterations:* For pharyngeal maximum pressure, the assumption of normality was violated for both saliva and water swallows. Results of the Friedman's test indicated that during the UES pressure manipulation task, the pharyngeal maximum pressure did not significantly change across time for saliva swallows ( $\chi^2(3) = 1.8, p = .61$ ), and for water swallows ( $\chi^2(3) = 1.8, p = .61$ ). At session 1, there was no significant difference in the pharyngeal maximum pressure during manipulation compared to no manipulation for saliva swallows ( $p = 1$ ) with a median pharyngeal maximum pressure during manipulation of 109.50 mmHg and of 113.09 mmHg during no manipulation. Further, there was no significant difference for water swallows ( $p = .69$ ) with a median pharyngeal maximum pressure of 116.92 mmHg during manipulation and 109.82 mmHg during no manipulation.

For analysis of pharyngeal normalised for saliva and water swallows, the assumptions of homoscedasticity and normality of the residuals were not met. Results of the Friedman's test indicated that the pharyngeal normalised time did not significantly change across time during the UES pressure manipulation task for saliva swallows ( $\chi^2(3) = 1, p = .80$ ), and for water swallows ( $\chi^2(3) = 6.6, p = .09$ ). At session 1, no significant difference was found for the pharyngeal normalised time of saliva swallows ( $p = .31$ ) with a median pharyngeal normalised time of 32.09 ms/cm during manipulation and 30.18 ms/cm during no manipulation. There was no significant difference for water swallows ( $p = .56$ ) with a median pharyngeal normalised time of 57.56 ms/cm during manipulation and of 61.67 ms/cm during no manipulation.

#### 9.3.2.3. *Qualitative Analysis*

The following categories summarise the techniques applied by the participants to prolong UES opening duration:

- change of pressure amplitude (e.g. to swallow gently or effortful),
- change of timing of pressure generation (e.g. to swallow slower or faster),
- manipulation of other muscles (e.g. to stabilise the abdominals),
- visualisation (e.g. to visualise a relaxed UES),
- imagination (e.g. to swallow a big marshmallow),
- relaxation (e.g. to relax the UES at the end of a swallow),
- focus on biofeedback, other techniques (e.g. negative practice),
- or no strategy found.

No most helpful strategy overall was mentioned by more than one participant.

### 9.4. Discussion

This is the first research programme to evaluate *direct* pressure modulation at the UES in healthy subjects. It is critical to understand the potential for pressure modulation at the UES in healthy subjects first. These data provide a foundation for future research evaluating the potential for behavioural modulation in patients with impaired UES resting pressure. Data regarding the potential of healthy subjects for *direct* modulation of pressure relaxation during swallowing provides a foundation for future studies assessing this in patients with impaired pressure relaxation during swallowing.

It was hypothesised that healthy adults would be able to behaviourally increase UES resting pressure following biofeedback training. There was evidence of task-specific volitional increase of UES resting pressure following biofeedback training; however, increased UES

resting pressure was associated with pharyngeal pressure generation in some - yet the minority - of the participants. The hypothesis that subjects would be able to decrease UES resting pressure following training was refuted by the data; no evidence for purposeful decrease in resting pressure was found. Further, it was hypothesised that subjects would be able to behaviourally prolong pressure related UES opening duration during swallowing following training without associated change in pharyngeal pressure. The findings aligned partly with this hypothesis. The results indicate that participants were able to behaviourally prolong pressure related UES opening for saliva and water swallows using visual biofeedback; this was accomplished without change in pharyngeal pressure. However, performance was not enhanced by daily practice. Different findings for the non-swallowing and swallowing task indicate that pressure at rest and during swallowing are separate phenomena with different underlying control mechanisms.

#### ***9.4.1. Behavioural Modulation of UES Resting Pressure***

##### *9.4.1.1. Increase of UES Resting Pressure*

Evidence for increased UES resting pressure suggests a potential of healthy adults to amplify contraction of the UES muscles; practice appears to be required for development of strategies for direct pressure manipulation. Higher UES resting pressure values were achieved after the first week but not after the second week of training; no increased pressure after the second week may reflect a ceiling effect or training fatigue. Analysis of normalised UES resting pressure further revealed a significant pressure increase at the follow-up; analysis of non-normalised pressure was close to significance. This pressure increase suggests that the subjects overcame practice fatigue during the training break. The findings of this study support data in the literature reporting that UES resting pressure in healthy subjects is susceptible to different variables. An increase in resting pressure in healthy subjects has been reported due to emotional stress (Cook et al., 1987), during inspiration (Eastwood et al., 2007; Kahrilas et al., 1987), during phonation (Perera et al., 2008), and during times of frequent swallowing (DiRe et al., 2001). Further, an increase in resting pressure has been documented secondary to pharyngeal stimulation with water (Shaker et al., 1997).

##### *9.4.1.2. Decrease of UES Resting Pressure*

Lacking evidence for purposeful decrease of UES resting pressure suggests no potential of healthy adults to disrupt contraction of the UES muscles (Jungheim et al., 2014a; Lang, 2013). Further, an inability to volitionally reduce UES resting pressure may be explained by factors

such as pressure generation due to intrinsic muscular characteristics of the UES (S. Singh & Hamdy, 2005) or distention caused by the presence of the intraluminal catheter (Jungheim, Schubert, et al., 2015). Also, there might be a flooring effect in healthy subjects, in whom physiology mandates a minimum degree of resting pressure to fulfil the barrier function between the pharynx and oesophagus. Resting pressure has been shown to decrease during sleep (Eastwood et al., 2007; Kahrilas et al., 1987). However, while various variables have been reported in the literature that may increase UES pressure, there is comparatively little research documenting factors associated with a pressure decrease in healthy subjects.

Notably, normalised resting pressure during efforts to decrease resting pressure at the first session and at the follow-up was significantly different compared to baseline measures. However, this difference reflected a pressure increase rather than a decrease. The participants' attempt to relax the UES muscles may have resulted in fortified muscle contraction, or more likely, considering the significant drop in natural pressure at the follow-up, this increase in UES resting pressure might not reflect a true pressure rise.

Different outcomes for the contraction and relaxation task indicate that volitional pressure increase and decrease need to be analysed separately. Future research will clarify the potential of patients with impaired UES resting pressure to modulate resting pressure. If consistent findings to this study would be revealed, this may indicate limitations in behavioural treatment approaches for patients with pathological UES resting pressure.

#### 9.4.1.3. *Change in Non-manipulated UES Resting Pressure*

There was a significant drop in non-manipulated UES resting pressure at the follow-up that may reflect an effect of training. However, if performance was generalised to non-manipulated resting pressure, higher rather than lower pressure values seem more obvious. More likely, the difference reflects considerable within-subject variability of resting pressure as reported in the literature (Jungheim et al., 2014b). Further, differences in non-manipulated resting pressure over time may indicate altered strain related to catheter placement. Stress related to catheter placement would be more likely at the commencement of training. With daily practice, participants may become more acquainted with the procedure, which might be mirrored in lower non-manipulated UES resting pressures at the end of the study protocol (Cook et al., 1987). The effect of acquaintance with the procedure on data may be an interesting avenue for future research.

When interpreting changes in pressure amplitude it is important to consider that there is intra-individual variability in natural UES resting pressure (Jungheim et al., 2014b). Consequently, altered resting pressure due to volitional manipulation cannot be separated from pressure changes related to other factors such as the subject's emotional status (Cook et al., 1987) or respiration (Kahrilas et al., 1987).

There was some evidence that efforts to contract the UES muscles at rest were associated with pressure generation in the pharynx. The questions answered by the participants provided further insight into the specificity of pressure manipulation. Some techniques applied during attempts to increase resting pressure implied non-specific pressure manipulation; such techniques involved contraction of muscles other than the UES muscles. Differently, strategies such as visualisation techniques may be more discrete.

#### ***9.4.2. Behavioural Modulation of UES Opening Duration***

Participants were able to behaviourally prolong pressure related UES opening for saliva and water swallows without training. This suggests that participants may have an inherent but restricted capacity to increase UES opening duration; thus, training is not necessary for maximal performance. The restricted capacity to prolong UES opening duration may be explained by the fact that UES opening is one single aspect of pharyngeal swallowing that is sequenced by the CPG in the brainstem (Ertekin & Aydogdu, 2003; Humbert & German, 2013; Vasant & Hamdy, 2013). Interestingly, the ceiling effect on performance is consistent with newer research reporting no effect of the Mendelsohn manoeuvre on UES opening duration in healthy adults. Doeltgen and colleagues (2017) studied the effects of the Mendelsohn manoeuvre in 12 healthy adults using HRIM and reported no difference in UES opening duration, whether participants swallowed naturally or executed the manoeuvre. Inamoto and colleagues (2018) evaluated the effect of the Mendelsohn manoeuvre in nine healthy adults using 320-row area detector CT. They also reported no prolongation of UES opening duration during execution of the Mendelsohn manoeuvre.

Further, results indicate that prolonged UES opening duration was achieved without change in pharyngeal pressure patterns. However, considering the strategies described, some techniques imply biomechanical or pressure manipulation of the swallow in its entirety rather than direct pressure modulation of the UES opening duration. Such strategies involve altered effort during swallowing or involvement of muscles other than the UES sphincter muscles. Hence, further research is needed to clarify whether UES pressure modulation during swallowing can be

achieved without associated change of other swallowing biomechanics not measured in this study. If this would be possible, the specificity in rehabilitation of UES impairment may be increased.

#### ***9.4.3. Limitations and Future Research***

Limitations of this research are acknowledged. The small sample size potentially impacted statistical analyses. For example, a small sample may affect validity of checking the assumptions for data analysis using linear mixed effects models. The large confidence intervals of estimated UES resting pressure at the analysed sessions are not surprising in the context of the small sample size. Hence, the research findings need to be interpreted in the context of exploratory research; future research is indicated to investigate the potential for direct UES pressure manipulation in larger samples of healthy participants. Notably, the majority of participants recruited for this project were under the age of 35 years and all subjects were female. Thus, caution is warranted when generalising findings to male subjects and participants of advanced age. In future studies, the cohort should involve both females and males and subjects of a wider age range.

Limitations of the technology are acknowledged. In the course of the project, an increasing number of catheter sensors malfunctioned. Defect sensors do not record real pressure, but instead, provide interpolated pressure estimates. For analysis, there are the options of including or excluding data recorded by defect sensors. If sensors are excluded from analysis, information is missing, and results may be misleading. If interpolated data is included, real data is mixed with non-real data, which may result in different misinterpretations of the data. The vulnerability of solid-state catheters has been previously reported (Bredenoord & Smout, 2008; S. Meyer et al., 2012). Potential technical enhancements in the future would contribute to optimised use of HRM. Further, reliability findings revealed moderate to good reliability for the outcome measures. The data suggest that sensor selection of the UES and pharynx affected reliability. Hence, automated sensor selection may increase reliability. However, there are limited automated analysis options embedded into ManoView™ for pharyngeal swallowing and customised external analysis methods decrease the comparability of data across studies. Further investigation of measurement reliability of HRM is warranted.

Limitations specific to the study investigating modulation of UES resting pressure include the lack of counterbalance of the pressure increase and pressure decrease tasks. Hence, results may be confounded by task order effects. It cannot be excluded that following muscle contraction,



muscle relaxation may have been impeded. As catheter placement may contribute to emotional stress, data collected following catheter placement may be increased compared to outcome measures collected at the conclusion of a session (Cook et al., 1987). However, the adjustment period following catheter placement allowed subjects to relax prior to data collection; thus, confounding effects on the data were likely prevented.

Limitations specific to the study evaluating volitional prolongation of UES opening include restrictions in immediate visual biofeedback. Since UES opening duration is short, a zoom-in function of ManoView™ was used to make the opening period distinctly visible on the HRM display panel. However, with greater zoom, recordings move faster on the display. The increased speed of displayed recordings likely made it more difficult for participants to visually capture UES opening duration. Further, participants could not easily compare UES opening durations of consecutive swallows, as they were not displayed concurrently on the monitor. Additionally, manipulated UES opening duration differed minimally within a subject across swallows; hence, registering differences visually was likely challenging. Considering these limitations, immediate manometric biofeedback may be more suitable for manipulation of pressure amplitude seen as colour alterations, rather than for modulation of UES opening duration. Yet, performance for the task to prolong UES opening duration was likely still supported by the colour plots by making the task goal more tangible than if verbal instructions were used exclusively. Additionally, the colour plots provided visual feedback regarding pressure changes in the pharynx. A further limitation is that the findings need to be interpreted in the context of non-parametric analyses which entail the risk of not detecting a potential true effect (low power) (Field et al., 2012).

The findings of this study inform about pressure changes in the pharynx and about applied manipulation strategies while other potential alterations of the swallowing response were not assessed. The addition of imaging modalities, such as videofluoroscopy, in future studies could reveal information about potentially altered swallowing biomechanics during performance. It is critical to understand the potential of healthy subjects for pressure modulation in the absence of altered pharyngeal pressure generation and altered swallowing biomechanics as modulation of the entire swallowing response may have negative impacts on swallowing safety and efficiency.

To assess change in performance without training, a control group may be included in a follow-up study. Further, future research is warranted to investigate the role of biofeedback in task

performance. To understand the potential for internalisation of task performance, additional analyses of performance with no biofeedback are required in future studies. The use of brain imaging techniques in follow-up studies may provide insight into cortical control mechanisms during behavioural pressure manipulation. Further, ongoing research is needed to evaluate whether achieved pressure alterations during manipulation are functionally relevant. It could be argued that manipulated pressure need to reach values above or below the normal range of UES resting pressure; hence, normative data are needed as a reference. To serve as a suitable reference, normative data should be acquired using the same catheter diameter, as the size of the catheter in situ may affect data (Nativ-Zeltzer et al., 2016). However, there is no published normative data collected with the catheter diameter used in this research. Thus, as discussed in Chapter 8, there is a need for further development of normative data. Reports of normative data of UES resting pressure collected with catheters of different width show large standard deviations (Jungheim, Schubert, et al., 2015; S. Meyer et al., 2012), suggesting that the extent of pressure modulation would likely need to be considerably high to reach values outside of the range of reported norms. Further, future research is warranted to evaluate the functional significance of increased UES opening duration. Adjunctive impedance analysis may clarify effects of manipulated UES opening duration on bolus flow, a critical aspect for efficient and safe swallowing.

Ongoing research is needed to further clarify the potential for purposeful pressure manipulation at the UES at rest and during swallowing in healthy subjects to understand the capacity of a healthy system for pressure modulation. Future studies may elucidate if impaired pressure regulation at rest and during swallowing may be behaviourally targeted in patients. Such studies will increase our understanding of clinical implications of pressure modulation. For example, patients with globus symptoms may present with increased UES resting pressure, also referred to as basal pressure (Corso et al., 1998; L. Peng, Patel, Kushnir, & Gyawali, 2015; Schindler et al., 2013; Tokashiki, Funato, & Suzuki, 2010) or dysphagic patients may show decreased UES resting pressure (L. Peng et al., 2015). Current behavioural treatment options for UES dysfunction during swallowing involve alterations of pharyngeal biomechanics, yet a change of the entire swallowing response may negatively impact individual aspects of swallowing (Garcia, Hakel, & Lazarus, 2004). Thus, further research is indicated to evaluate purposeful pressure modulation intra-swallow in patient populations with UES dysfunction to clarify if the specificity in behavioural treatment for UES impairment may be increased.

Further, ongoing research is key to investigate whether different components of a partially brainstem driven swallowing response can be purposefully modulated in healthy individuals. Increased understanding of the role that cortical and subcortical structures may play in control of swallowing will be essential in the development of rehabilitation approaches of impaired swallowing (Humbert & German, 2013). However, it is acknowledged that healthy subjects may be less able to modulate pharyngeal swallowing than patients with dysphagia. Healthy swallowing is a maximally functional behaviour; thus, volitional modulation may imply a potential functional compromise. Patients with dysphagia present a compromised functional behaviour; hence, increased functionality may be achieved with purposeful modulation.

## **PART IV: SUMMARY AND CONCLUSIONS**

## **10. Summary and Conclusions**

### **10.1. Methodological Studies**

Assessment of UES function relies on refined use of instrumentation. Accurate UES evaluation is pivotal as failed diagnosis of dysfunction may negatively impact patients' swallowing safety and efficiency. Further, detailed diagnosis of UES dysfunction is paramount as it guides rehabilitation. This research addresses the need for continuing enhancement in instrumental UES assessment. Aspects such as validity, reliability, and methodology of data acquisition and data analysis of instrumentation used for UES examination are important to consider.

Validity and reliability of a pocket-sized ultrasound system in the non-radiological assessment of hyolaryngeal excursion was explored to evaluate the potential for clinical use of this new technology. While there is data in the literature to suggest that larger, more expensive ultrasound systems provide valid and reliable swallowing measures, this was not confirmed in our study for the pocket-sized Clarius™ system. Given the utmost importance of validity and reliability of instrumentation used for diagnostic purposes, the clinical use of the Clarius™ system for swallowing assessment is not indicated at this time. Further research is required to clarify whether our findings reflect technical limitations of the Clarius™ system or of pocket-sized technology more generally. Further, ongoing research is needed to confirm validity and reliability of larger ultrasound devices. This will further elucidate if ultrasound may be used in routine clinical assessment of swallowing.

Application of pharyngeal HRM/HRIM for swallowing assessment is rapidly emerging in research and clinical settings. Importantly, there is growing evidence in the literature that methodology impacts the interpretation of findings. However, there are insufficient methodological standards available for data acquisition and data analysis. This is reflected in the findings of the systematic review that revealed significant variability in methodology of data acquisition and data analysis for pharyngeal HRM and HRIM. This methodological variability has implications for interpretation of published data and for the clinical use of this instrumentation. Clinicians and researchers need to be alert when comparing findings from different studies; data comparison is limited if methodology of data acquisition and/or data analysis differs. Considering that data derived from HRM/HRIM build the foundation for clinical decisions regarding treatment of UES dysfunction, such as surgical interventions, the need for refined and more standardised methods is paramount.

## **10.2. Behavioural Study**

Current behavioural treatment options for UES dysfunction, particularly for impaired UES pressure regulation, are limited. Existing behavioural treatment approaches target UES function indirectly via alteration of swallowing biomechanics or of swallowing pressure. This research provides first data to increase our understanding of the potential of healthy subjects to more directly modulate pressure generation at the UES. Findings provide evidence that subjects are able to purposefully increase UES resting pressure using visual biofeedback. This UES pressure modulation was achieved, by the majority of the subjects, without associated pressure generation in the pharynx. Interestingly, no evidence for volitional decrease of UES resting pressure was found. Further, our data indicate that healthy subjects are able to behaviourally prolong pressure related UES opening during swallowing without changing pharyngeal pressure patterns, using visual biofeedback. Data of this study may provide grounds for future research exploring potential behavioural treatment options for UES impairment. If pressure at the UES could be directly targeted in patients with impaired pressure regulation at the UES, the specificity of behavioural treatment options may be increased. Specific pressure UES modulation may be particularly relevant in patients in whom modulation of swallowing biomechanics negatively impacts swallowing safety or efficiency.

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## **APPENDICES**

## Appendix A: Information Sheets and Consent Forms



### Participant Information Sheet

#### Research Title

Ultrasonic assessment of swallowing in healthy adults

#### Principal investigator

Katharina Sophie Winiker

PhD Candidate, Dept. of Communication Disorders, University of Canterbury

Rose Centre for Stroke Recovery and Research

St George's Medical Centre, Leinster Chambers, Level One

249 Papanui Road, Merivale, Christchurch 8014

(03) 369 2385

#### Supervisors

Prof Maggie-Lee Huckabee

Dept. of Communication Disorders, University of Canterbury

Rose Centre for Stroke Recovery and Research

Dr Phoebe Macrae

Rose Centre for Stroke Recovery and Research

Dr Kristin Gozdzikowska

Rose Centre for Stroke Recovery and Research

#### Aims of the research project

To increase our understanding of normal swallowing, the study investigates how the muscles under the chin and in the throat contribute to two crucial events during swallowing: directing food to enter into the esophagus from the throat, and protecting from food entering the airway (commonly referred to as “going down the wrong pipe”). The study also investigates a new

way of assessing swallowing using ultrasound imaging. This technique is used routinely in healthcare to diagnosis illnesses or to image infants in their mother's womb. Ultrasound is safe, non-invasive, and relatively inexpensive. Before we can use ultrasound imaging to identify swallowing problems in patients, we need to assess normal swallowing and study if ultrasound provides reliable and valid measures.

### **Participant selection**

You can be selected for this study if you are at least 20 years old. Exclusion criteria include history of swallowing difficulties, neurological or muscular disease, head and neck tumour or structural abnormalities of the head and neck region, drugs which might have an impact on swallowing, pregnancy, or allergy to any of the offered foods.

### **Research procedure**

You will attend two sessions at the Rose Centre for Stroke Recovery and Research at St George's Medical Centre (249 Papanui Rd). If you agree to participate in the study:

- You will come to the Swallowing Lab in the Rose Centre in total two times (the two sessions need to be three weeks apart). Each session will last approximately 2½ hours.
- First, you will be provided a consent form which you can review at your own pace, and can sign if you agree to the study / meet the criteria to participate.
- In the first session, you will be seated comfortably in a chair and the researcher will make ultrasound measurement from the front of your throat while you are sitting still or swallowing (approximately 36 measures in total). An ultrasound transducer will be placed on the skin surface below your chin and above the larynx (Adam's apple); this ultrasound technique is the same as what is used on pregnant women. A further six swallows will be completed using ultrasound during a motion picture x-ray of your swallowing (termed videofluoroscopic swallowing study).
- In the second session, you will again sit still or swallow (approximately 45 measures in total) during ultrasound imaging. The same measures will be repeated with the exception of the x-ray.

## **Participation**

If you agree to take part in this study, you are free to withdraw at any time without stress, embarrassment or difficulty, and without having to give a reason. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue. You can withdraw your data any time before the time of analysis.

## **Risks and Benefits**

There is no direct benefit to you; however, your participation gives important information about swallowing and a new swallowing assessment instrumentation. To cover the cost of participation (travel and parking) you will receive a petrol voucher of \$20.

Ultrasound is used as a clinical instrumentation in a broad medical field, such as for pregnancy scan. The technique does not include any health risks. Videofluoroscopy, which is the gold-standard in assessing swallowing, is an X-ray examination and involves radiation exposure. It is known that radiation exposure in excessive quantities might increase the long-term risk of developing cancer. To limit radiation exposure, we will apply only a low dose and the exposure time will be limited to less than 3 minutes. Additionally, you will wear lead aprons for protection of your internal organs. Low-dose settings will be used. Using these settings, one could have up to 40 of these studies in a year without exceeding the safe dose limit.

Facilities for emergency medical management, including suctioning and intubation, are available in the Swallowing Research Laboratory where the sessions take place. Further medical help is available from the medical team at the hospital should any complications arise. In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigator. If you have questions about ACC, contact your nearest ACC officer or the investigator.



## **Confidentiality**

Videofluoroscopy involves video-recording of your swallowing including visualization of the internal structures of the head and neck region (e.g., muscles and bones). Ultrasonic images will include anatomical structures of your lower chin and parts of the throat. The recorded data from ultrasound and videofluoroscopy will measure the distance between structures in your throat as they move during swallowing. The data will be included in the investigator's PhD thesis and might be submitted for publication to a peer-reviewed journal. However, no material which could personally identify you will be used in any reports on this study. Confidentiality will be assured by giving you a coded identification number. Consent forms containing your name will be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored in the locked Swallowing Lab at the Rose Centre for Stroke Recovery and Research for a period of 10 years, at which time they will be destroyed. With your permission, data from this study may be used in future related studies, which have been given ethical approval from Human Ethics Committee. It is possible that data will provide the foundation for a subsequent research trial.

## **Results**

You will be offered a copy of the final manuscript of this project or a summary. However, you should be aware that a significant delay may occur between completion of data collection and the final report.

## **About the investigators**

Katharina Winiker has been a PhD candidate at the University of Canterbury since February 2016 who has a Bachelor degree in Speech and Language Therapy from University Fribourg in Switzerland. She has worked as a clinician in intensive care unit, acute and rehabilitation hospitals in Switzerland for six years.

Prof Maggie-Lee Huckabee has a Ph.D. in Speech Pathology. She practiced as a clinician for 13 years. She is now professor in the Department of Communication Disorders and Director of the Rose Centre for Stroke Recovery and Research.

Dr Phoebe Macrae has a Ph.D. in Speech Pathology and is the Deputy Director, Rose Centre for Stroke Recovery and Research.

Dr Kristin Gozdzikowska has a Ph.D. in Speech Pathology. She works as a clinician and is a post-doctoral fellow at the Rose Centre for Stroke Recovery and Research.

## Questions

You can contact the principal investigator if you require any further information about the study. The principal investigator, Katharina Winiker, can be contacted during work hours (03) 369 2385 or via email: [katharina.winiker@pg.canterbury.ac.nz](mailto:katharina.winiker@pg.canterbury.ac.nz)

If you need an interpreter, this can and will be provided.

If you have any questions or concerns about your rights as a participant in this research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.: Telephone: 0800 555 050 / Email: [advocacy@hdc.org.nz](mailto:advocacy@hdc.org.nz)

This study has been reviewed and approved by the UC Human Ethics Committee. If you have any questions or concerns regarding the ethical aspects of this study please contact the Human Ethics Committee: Telephone: 45588 or 03 364 2987 / Email: [human-ethics@canterbury.ac.nz](mailto:human-ethics@canterbury.ac.nz)



Department of Communication Disorders  
 Telephone: (03) 369 2385  
 Email: [katharina.winiker@pg.canterbury.ac.nz](mailto:katharina.winiker@pg.canterbury.ac.nz)



## Biomechanics of swallowing in healthy adults

### Consent Form

<input type="checkbox"/>	I have been given a full explanation of this project and have had the opportunity to ask questions.
<input type="checkbox"/>	I understand what is required of me if I agree to take part in the research project.
<input type="checkbox"/>	I understand that participation is voluntary and I may withdraw at any time without explanation and penalty. Withdrawal of participation will also include the withdrawal of any data or information I have provided.
<input type="checkbox"/>	I understand that any information I provide will be kept confidential to the researcher and his supervisors and that any published or reported results will not identify the participants. I understand that a PhD Thesis is a public document and will be available through the UC library.
<input type="checkbox"/>	I understand that all the data collected for the study will be kept in secure facilities and in password protected electronic form and will be destroyed after ten years.
<input type="checkbox"/>	I agree that the data might be used for future studies.
<input type="checkbox"/>	I understand the risk associated with taking part and how they will be managed.
<input type="checkbox"/>	I understand that I am able to receive a report on the findings of the study by contacting the researcher at the conclusion of the project.
<input type="checkbox"/>	I understand that I can contact the researchers Katharina Winiker ( <a href="mailto:katharina.winiker@pg.canterbury.ac.nz">katharina.winiker@pg.canterbury.ac.nz</a> / (03) 369 2385) or supervisor Maggie-Lee Huckabee ( <a href="mailto:maggie-lee.huckabee@canterbury.ac.nz">maggie-lee.huckabee@canterbury.ac.nz</a> / (03) 36 9 5124) for further information. If I have any complaints, I can contact the Chair of the University of Canterbury Human Ethics Committee, Private Bag 4800, Christchurch ( <a href="mailto:human-ethics@canterbury.ac.nz">human-ethics@canterbury.ac.nz</a> ).
<input type="checkbox"/>	I would like a summary of the results of the project.
<input type="checkbox"/>	By signing below, I agree to participate in this research project.

Name:.....

Signature:.....

Email address: .....

Date:.....

Research ID:.....

# Information Sheet

## Research Title

The capacity for volitional control of the upper oesophageal sphincter in healthy adults

## Principal investigator

Katharina Sophie Winiker  
MSc Candidate, Dept. of Communication Disorders  
University of Canterbury  
Rose Centre for Stroke Recovery and Research  
St George's Medical Centre  
Leinster Chambers, Level One  
249 Papanui Road, Merivale  
Christchurch 8014  
+64 3 364 2307

## Supervisors

Prof. Maggie-Lee Huckabee  
Dept. of Communication Disorders  
University of Canterbury  
Rose Centre for Stroke Recovery and Research  
  
Dr. Kristin Lamvik  
Dept. of Communication Disorders  
University of Canterbury  
Rose Centre for Stroke Recovery and Research

## **Aim of the research project**

You are invited to participate in a research project investigating how much control a healthy individual can have over reflexive parts of their swallowing. The aim of the study is to see if healthy adults can learn to change pressure at the “upper oesophageal sphincter” (UES). This muscle is located at the bottom of the throat and the top of the food tube, also called the oesophagus. Normally, this muscle is controlled reflexively. We want to investigate if healthy adults can learn to change this muscle volitionally through intensive training using visual feedback. It is important to better understand how the brain controls swallowing as this knowledge may help us plan treatment for patients with swallowing difficulties.

Pressure within the sphincter muscle will be measured using a technique called high resolution manometry (HRM). This is done with a thin, flexible tube that contains sensors which can measure pressure. This tube will be passed through the nose and the throat to the upper end of the food tube. During the training, you can observe the pressure changes on a live recording and try to change pressure by changing the colours on the display.

## **Participant selection**

You can be selected for this study if you are at least 18 years old, and have no history of swallowing difficulties, neurological or muscular disease, gastrointestinal issue/reflux or drugs which might have an impact on swallowing. Furthermore, participants with a history of frequent fainting, nosebleed or nosebleed that is not self-limiting will be excluded.

## **Research procedure**

The training will take place at the Rose Centre for Stroke Recovery and Research in Merivale. If you agree to participate in the study:

- You will get a consent form which you will sign if you agree to the study and meet the criteria to participate.
- You will come to the Swallowing Lab in the Rose Centre in total 11 times: The training will take place every work day for two weeks (10 sessions) and there will be a follow-up session after a two week break of no training.
- You will be shown colour images of pressure recordings at the sphincter muscle at the beginning of the first session and the training task will be explained.

- Once you feel comfortable and understand the goals, the catheter that measures pressure will be placed in your throat. To do this, you will be seated in a chair and the investigator will place a thin tube in your nose. As the tube reaches the top of your throat, you will be instructed to “swallow” the catheter with water. Once the end of the tube reaches the top of your food tube, it will be fixed with tape on your nose.
- The study includes two different tasks. Which task you will perform will randomly be selected. Depending on the task, you will:
  - First be asked to be as relaxed as possible for two minutes. Then you will be shown a screen displaying colour images representing pressure at the sphincter muscle. Then you will be asked to change the colour on the display to a colour that is as warm as possible for two minutes. After a break of two minutes, you will try to change the colour to a colour that is as cool as possible.
  - First be asked to swallow saliva five times. When we swallow, the sphincter muscle relaxes for a very short moment. This relaxation period is displayed on the screen as a dark blue area. During blocks of two minutes, you will be asked to increase the duration of this dark blue area when swallowing saliva. Between these blocks, you will make a break.
- The training (independent which task you will perform) lasts approximately 45 minutes, so the sessions last around 1 hour in total. Three of the 11 sessions will last around 1 ½ hours, because we will include some tasks for outcome measures.
- After the training, the tube will be removed and you will be asked to answer a few questions on the computer about the task performance.

## **Participation**

If you agree to take part in this study, you are free to withdraw at any time, without having to give a reason. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue. As a participant, you can withdraw your data any time before the time of analysis.

## **Risks and Benefits**

There is no direct benefit to you; however, your participation gives important information about neural control of swallowing. To cover the cost for participation (travel and parking) you will get a petrol voucher of \$50.

The technique of high resolution manometry is used as a clinical tool and for research and as yet there are no side effects known (Knigge et al., 2014). You will be monitored very carefully by the researchers for any negative changes during your participation in this study. Facilities for emergency medical management, including suctioning and intubation, are available in the Swallowing Research Laboratory where the training is completed. Further medical help is available from the medical team at the hospital should any complications arise.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigator. If you have questions about ACC, contact your nearest ACC officer or the investigator.

### **Confidentiality**

There will be no audio- or video-recording of the session. The only recorded data will concern pressure. The data will be included in the investigator's Master thesis and might be submitted for publication to a peer-reviewed journal. However, no material which could personally identify you will be used in any reports on this study. Confidentiality will be assured by giving you a coded identification number. Consent forms containing your name will be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored in the locked Swallowing Lab at the Rose Centre for Stroke Recovery and Research for a period of 5 years, at which time they will be destroyed. With your permission, data from this study may be used in future related studies, which have been given ethical approval from Human Committee. It is possible that data will provide the foundation for a subsequent research trial.

## **Results**

You will be offered a copy of the final manuscript of this project or a summary in lay language. However, you should be aware that a significant delay may occur between completion of data collection and the final report.

## **About the investigators**

Katharina Winiker is a MSc candidate at the University of Canterbury who has a Bachelor degree in Speech and Language Therapy from University Fribourg in Switzerland. She has worked as a clinician in intensive care unit, acute and rehabilitation hospitals in Switzerland for six years.

Prof. Maggie-Lee Huckabee has a Ph.D. in Speech Pathology. She practiced as a clinician for 13 years. She is now professor in the Department of Communication Disorders and Director of the Rose Centre for Stroke Recovery and Research.

Dr. Kristin Lamvik has a Ph.D. in Speech Pathology. She works as a clinician and is part of the research team of the Rose Centre for Stroke Recovery and Research with a main focus on manometry studies.

## **Questions**

You can contact the principal investigator if you require any further information about the study.

The principal investigator, Katharina Winiker, can be contacted during work hours +64 3 364 2307 or via email: [katharina.winiker@pg.canterbury.ac.nz](mailto:katharina.winiker@pg.canterbury.ac.nz)

If you need an interpreter, this can and will be provided.

If you have any questions or concerns about your rights as a participant in this research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.: Telephone: 0800 555 050 / Email: [advocacy@hdc.org.nz](mailto:advocacy@hdc.org.nz)

This study has been reviewed and approved by the UC Human Ethics Committee. If you have any questions or concerns regarding the ethical aspects of this study please contact the Human Ethics Committee: Telephone: 45588 or 03 364 2987 / Email: [human-ethics@canterbury.ac.nz](mailto:human-ethics@canterbury.ac.nz)



## Consent Form

### The capacity for volitional control of the upper oesophageal sphincter in healthy adults

<input type="checkbox"/>	I have been given a full explanation of this project and have had the opportunity to ask questions.
<input type="checkbox"/>	I understand what is required of me if I agree to take part in the research project.
<input type="checkbox"/>	I understand that participation is voluntary and I may withdraw at any time without explanation and penalty. Withdrawal of participation will also include the withdrawal of any data or information I have provided.
<input type="checkbox"/>	I understand that any information I provide will be kept confidential to the researcher and his supervisors and that any published or reported results will not identify the participants. I understand that a Master's Thesis is a public document and will be available through the UC library.
<input type="checkbox"/>	I understand that all the data collected for the study will be kept in secure facilities and in password protected electronic form and will be destroyed after five years.
<input type="checkbox"/>	I understand the risk associated with taking part and how they will be managed.
<input type="checkbox"/>	I understand that I am able to receive a report on the findings of the study by contacting the researcher at the conclusion of the project.
<input type="checkbox"/>	I understand that I can contact the researcher Katharina Winiker ( <a href="mailto:katharina.winiker@pg.canterbury.ac.nz">katharina.winiker@pg.canterbury.ac.nz</a> / +64 3 364 2307) or supervisor Maggie-Lee Huckabee ( <a href="mailto:maggie-lee.huckabee@canterbury.ac.nz">maggie-lee.huckabee@canterbury.ac.nz</a> / +64 33642042) for further information. If I have any complaints, I can contact the Chair of the University of Canterbury Human Ethics Committee, Private Bag 4800, Christchurch ( <a href="mailto:human-ethics@canterbury.ac.nz">human-ethics@canterbury.ac.nz</a> ).
<input type="checkbox"/>	I would like a summary of the results of the project.
<input type="checkbox"/>	By signing below, I agree to participate in this research project.

Participant's name: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Date of birth: \_\_\_\_\_

Email: \_\_\_\_\_

Gender: \_\_\_\_\_

Research ID: \_\_\_\_\_

## Appendix B.1: Validity and Reliability of Ultrasound – Demographics of Study Participants

**Table B.1.** Demographics of study participants (n = 20)

<b>Age and sex</b>	<b>Ethnicity</b>	<b>Handedness</b>
<i>20 - 39 years:</i> 3 females, 2 males	<i>New Zealand European:</i> 17 subjects (85%)	<i>Right:</i> 19 subjects (95%)
<i>40 - 59 years:</i> 2 females, 3 males	<i>New Zealand European/Maori:</i> 1 subject (5%)	<i>Left:</i> 1 subject (5%)
<i>60 - 79 years:</i> 3 females, 2 males	<i>Chinese:</i> 1 subject (5%)	
<i>80+ years:</i> 2 females, 3 males	<i>Afro-Caribbean:</i> 1 subject (5%)	

## Appendix B.2: Validity and Reliability of Ultrasound - Ultrasound Guideline

### Ultrasound Guideline

**General:** apply soft contact pressure of the transducer on the skin

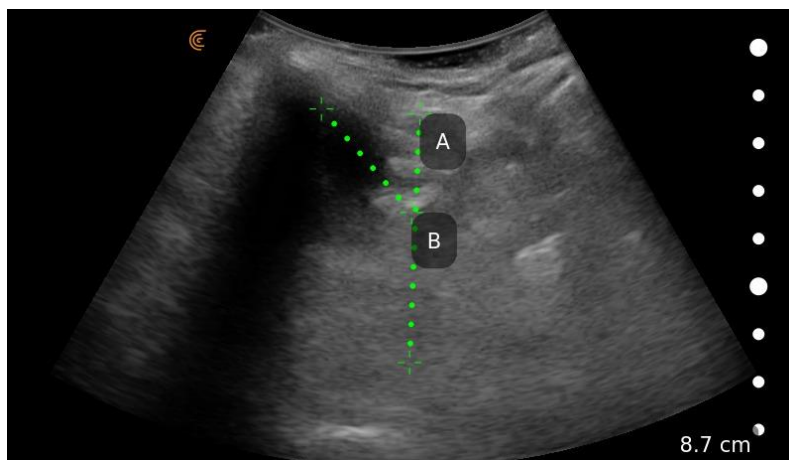
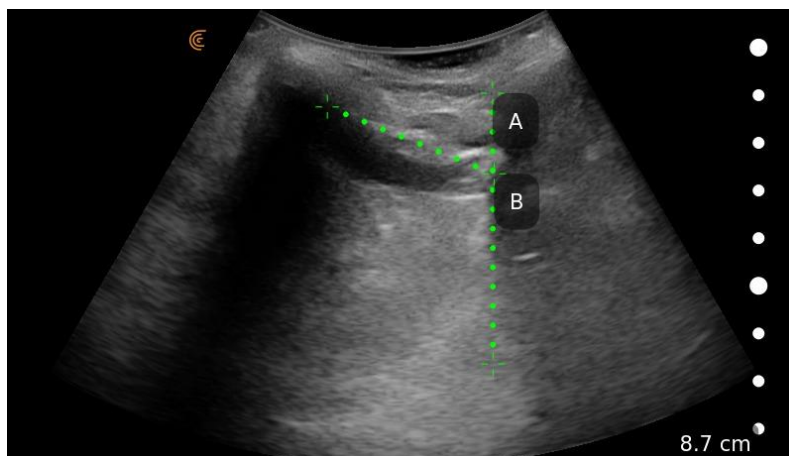
#### Hyoid excursion

*Transducer: Curvilinear, View: Mid-sagittal plane, submental placement*

*Comments: Rest measurement taken after swallowing*

Choose the two line measurement tool

1. Line A: draw a best fit line along the anterior border of the shadow of the hyoid bone.
2. Line B: place one calliper at the posterior border of the onset of the shadow created by the mandible. Place the other calliper at the intersection point with the best fit Line A at the onset of the shadow.



← Anterior

## Tongue thickness

*Transducer: Curvilinear, View: Mid-sagittal plane, submental placement*

*Comments: 5mL apple puree bolus held on the tongue*

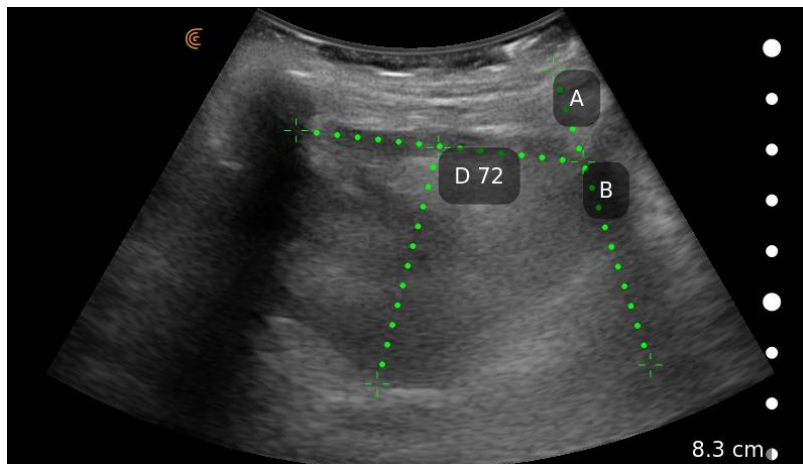
First, choose the two-line measurement tool

Same as for hyoid excursion:

1. Line A: draw a best fit line along the anterior border of the shadow of the hyoid bone.
2. Line B: place one calliper at the posterior aspect of the onset of the shadow created by the mandible. Place the other calliper at the intersection point with the best fit Line A at the onset of the shadow.

Then, choose the single line measurement tool

3. Calculate half of the mandible-hyoid distance (Line B)
4. Place one calliper of the single line at the intersection point of Line A and B. Place the other calliper at the halfway mark of Line B. Then move the calliper at the intersection point (of Line A and B) to the posterior edge of the bolus, 'point of triangle' (D72) (approximation of tongue to palate).



## Thyrohyoid approximation

*Transducer: Curvilinear, View: Mid-sagittal plane, anterior neck placement*

*Comments: Rest measurements taken after swallowing*

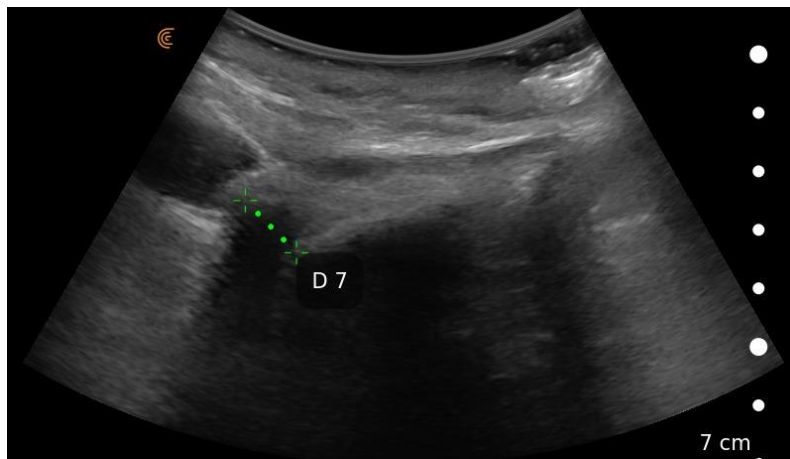
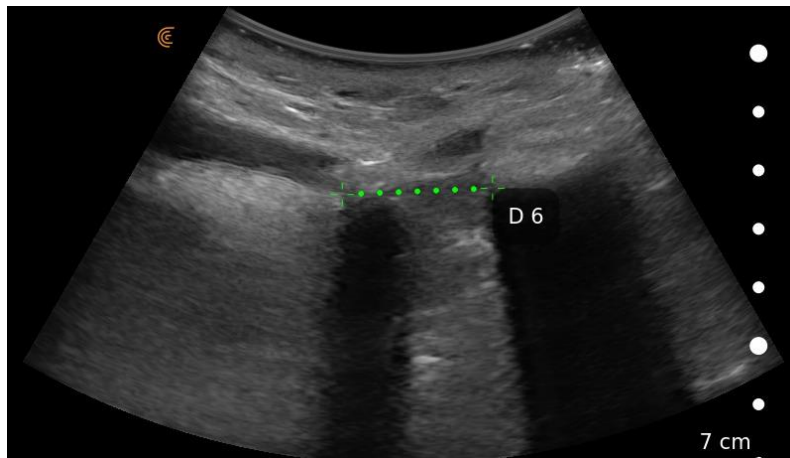
Choose the one-line measurement tool

For this measure, the overall rule is to find two consistently visible points for the hyoid bone and thyroid cartilage at rest and at maximal displacement. Within a participant, the aim is to be consistent. Across participants, it might differ slightly.

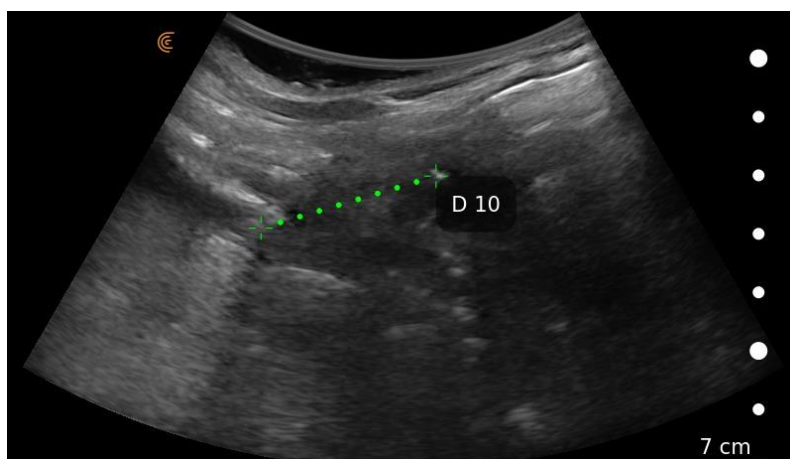
1. Line A: choose the single line tool and place one calliper at the beginning of the anterior border of the shadow of the hyoid if consistently visible at rest and at max OR at the hyoid opacity if consistently visible at rest and at max. This is the same point of measurement as used in measuring hyoid movement.
2. Line B: Place the other calliper at either the onset of the shadow of thyroid cartilage if consistently visible at rest and max OR at the bright opacity at the superior thyroid cartilage if consistently visible at rest and max.

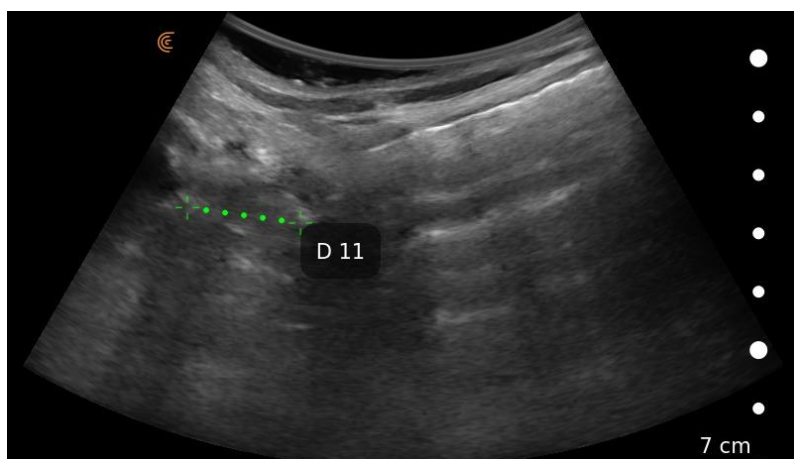
You may need to adjust the transducer slightly off midline to visualise thyroid structures or in participants with pronounced thyroid cartilages.

Example 1:

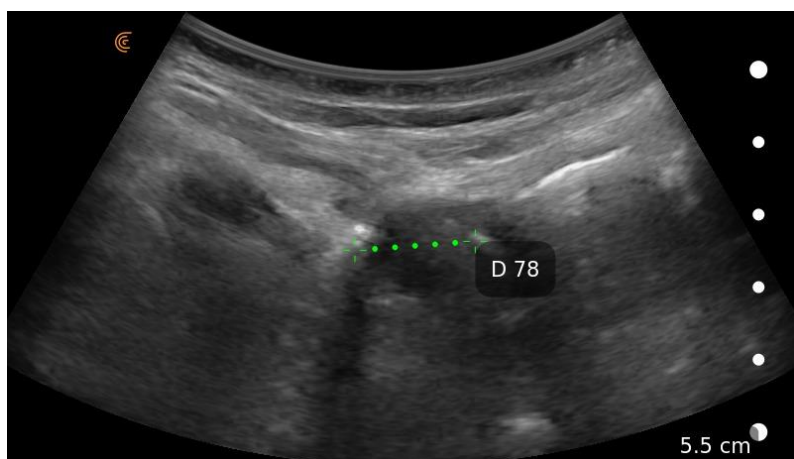
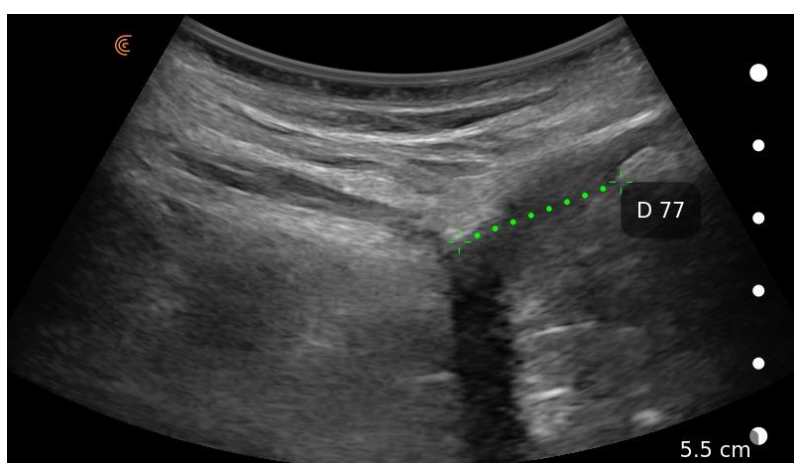


Example 2:





Example 3:



→ inferior

### Cross-sectional area of submental muscles

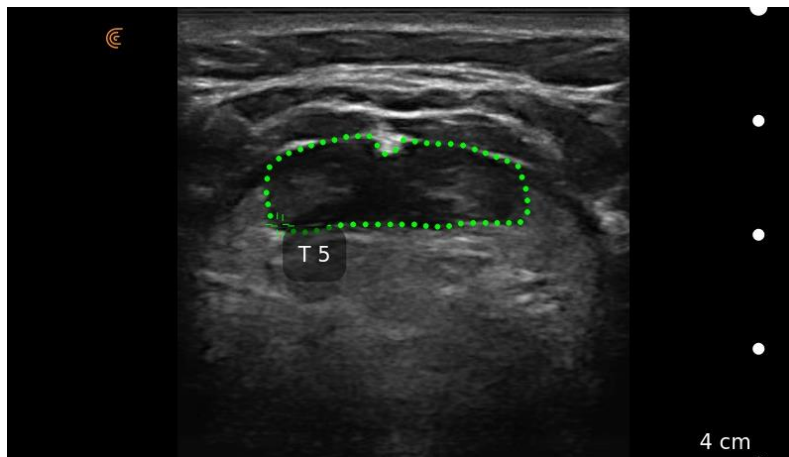
*Transducer: Linear, View: Coronal plane, submental placement*

*Comments: Scan anterior to posterior to find the largest and clearest boundaries for each muscle; you may require additional scanning for clear images or each muscle.*

Choose the freehand measurement tool

1. Geniohyoid\*: trace around outside of muscle INCLUDING the mylohyoid at the superior border only (do not include the mylohyoid at the left and right border); measure up to the opacity of connective tissue under the anterior belly of digastric muscles.

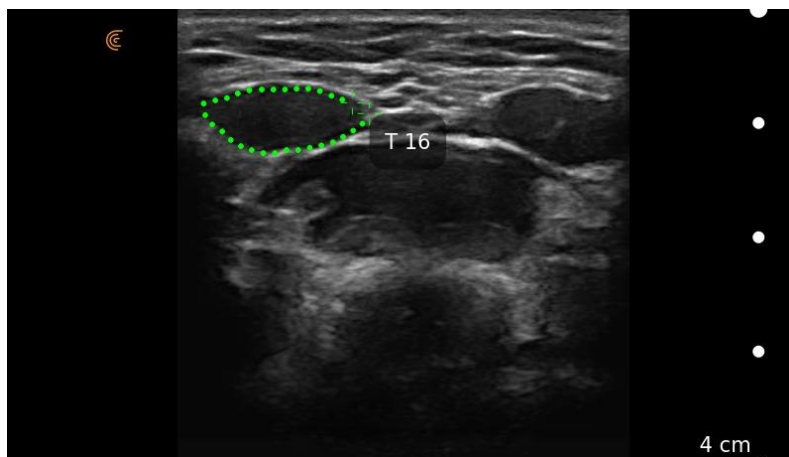
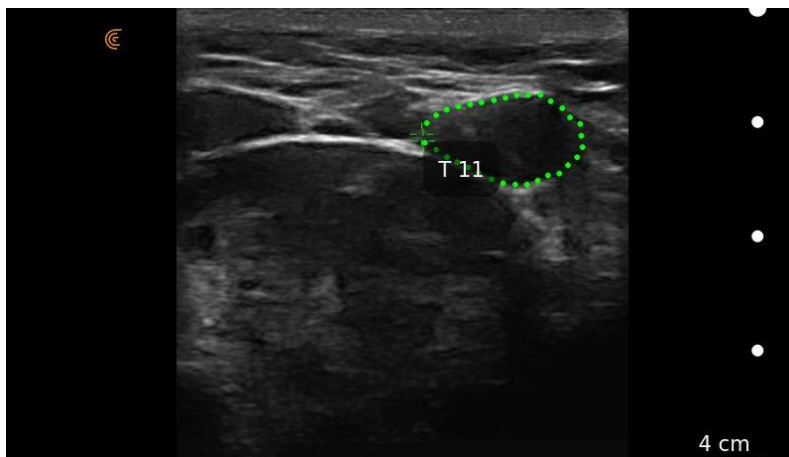
2. Left and right anterior belly of digastric: trace around outside of each muscle; *for left and right anterior belly of the digastric try to keep the plane (anterior-posterior) consistent. Be mindful that you keep the transducer with even pressure on the right and left muscles to minimise size difference from examiner error.*



superior



inferior



← participant's left

## Appendix B.3: Validity and Reliability of Ultrasound – Systematic Rater Error

**Table B.3.** Quantified systematic rater error for inter-rater reliability of ultrasonic data acquisition

Measure	Bolus	Error in the unit of measurement
Hyoid excursion	Dry, liquid, puree	Rater 3 < Rater 2 (-2.35 percentage change, $p < .001^*$ )
		Rater 3 < Rater 1 (2.79 percentage change, $p < .001^*$ )
Thyrohyoid approximation	Dry, liquid, puree	Rater 3 < Rater 2 (-7.52 percentage change, $p < .001^*$ )
		Rater 3 < Rater 1 (-4.16 percentage change, $p = .003^*$ )
		Rater 1 < Rater 2 (-3.36 percentage change, $p = .03^*$ )
Tongue thickness	Vanilla custard	Rater 2 > Rater 3 (1.90 mm, $p = .01^*$ )
GH <sup>+</sup>	-	[Rater 3 < Rater 1 (-58.01 mm <sup>2</sup> , $p < .001^*$ )]
		[Rater 3 < Rater 2 (50.09 mm <sup>2</sup> , $p < .001^*$ )]
FOM LAB	-	[Rater 3 < Rater 1 (-10.64 mm <sup>2</sup> , $p = .001^*$ )]
		[Rater 3 < Rater 2 (-9.32 mm <sup>2</sup> , $p = .002^*$ )]
RAB	-	[Rater 3 < Rater 1 (-10.67 mm <sup>2</sup> , $p < .001^*$ )]
		[Rater 3 < Rater 2 (-7.06 mm <sup>2</sup> , $p = .01^*$ )]

*Note.* \*significant at  $p \leq .05$ , FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles, [] = assumptions for analysis are not met



## Appendix B.4: Validity and Reliability of Ultrasound – Systematic Session Error

**Table B.4.** Quantified systematic session error for test-retest reliability of data ultrasonic data acquisition with reference session 1

Measure	Bolus		Systematic error (coefficient estimate, p-value)
Hyoid excursion	all		+ 2.55 percentage change, $p < 0.001^*$
FOM	LAB	-	- 8.72 mm <sup>2</sup> , $p = .02^*$
	RAB	-	- 7.12 mm <sup>2</sup> , $p = .01^*$

*Note.* \*significant at  $p \leq .05$ , FOM = floor of mouth muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

## Appendix B.5: Validity and Reliability of Ultrasound – Results

### Measurement Reliability (Video)

**Table B.5.1.** Intra-rater reliability for measurement (video) of Rater 1

Measure	Bolus	SEM (95% CI)	Between-subject SD
Hyoid excursion	Dry, liquid, puree	6.19 percentage change (5.32, 7.06)	5.60 percentage change
Thyrohyoid approximation	Dry, liquid, puree	11.26 percentage change (9.81, 12.95)	9.41 percentage change
Tongue thickness	Apple sauce	2.76 mm (2.02, 3.83)	4.82 mm
	Vanilla custard	1.85 mm (1.36, 2.55)	5.55 mm
	Olive oil	2.75 mm (2.02, 3.79)	6.10 mm
GH <sup>+</sup>	-	[33.08 mm <sup>2</sup> (24.34, 45.55)	53.53 mm <sup>2</sup> ]
FOM LAB	-	5.10 mm <sup>2</sup> (3.75, 7.02)	24.24 mm <sup>2</sup>
RAB	-	10.58 mm <sup>2</sup> (7.78, 14.57)	26.91 mm <sup>2</sup>

*Note.* SEM = standard error of measurement, CI = confidence interval, SD = standard deviation, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles, [] = assumptions for analysis are not met

**Table B.5.2.** Intra-rater reliability for measurement (video) of Rater 4

Measure	Bolus	SEM (95% CI)	Between-subject SD
Hyoid excursion	Dry, liquid, puree	4.82 percentage change (4.14, 5.50)	5.14 percentage change
Thyrohyoid approximation	Dry, liquid, puree	9.17 percentage change (7.99, 10.55)	6.17 percentage change
Tongue thickness	Apple sauce	2.76 mm (2.01, 3.83)	5.39 mm
	Vanilla custard	[3.00 mm (2.21, 4.13)	4.86 mm]
	Olive oil	2.63 mm (1.93, 3.62)	7.27 mm
GH <sup>+</sup>	-	20.86 mm <sup>2</sup> (15.35, 28.72)	48.78 mm <sup>2</sup>
FOM LAB	-	[9.94 mm <sup>2</sup> (7.32, 13.69)	17.85 mm <sup>2</sup> ]
RAB	-	12.57 mm <sup>2</sup> (9.25, 17.31)	16.79 mm <sup>2</sup>

*Note.* SEM = standard error of measurement, CI = confidence interval, SD = standard deviation, [] = assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

**Table B.5.3.** Inter-rater reliability for offline measurement (video)

Measure	Bolus	SEM (95% CI)	Between-subject SD
Hyoid excursion	Dry, liquid, puree	5.95 percentage change (5.14, 6.83)	5.29 percentage change
Thyrohyoid approximation	Dry, liquid, puree	10.30 percentage change (9.02, 11.92)	6.79 percentage change
Tongue thickness	Apple sauce	2.59 mm (2.10, 3.32)	5.28 mm
	Vanilla custard	2.76 mm (2.24, 3.51)	5.18 mm
	Olive oil	2.73 mm (2.22, 3.47)	6.24 mm
GH <sup>+</sup>	-	29.06 mm <sup>2</sup> (21.81, 41.59)	53.74 mm <sup>2</sup>
FOM LAB	-	[16.75 mm <sup>2</sup> (12.59, 24.12)	17.29 mm <sup>2</sup> ]
RAB	-	[20.66 mm <sup>2</sup> (15.54, 29.83)	17.19 mm <sup>2</sup> ]

*Note.* SEM = standard error of measurement, CI = confidence interval, SD = standard deviation, [] = assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

## Appendix B.6: Validity and Reliability of Ultrasound – Results

### Measurement Reliability (Image)

**Table B.6.1.** Intra-rater reliability for measurement (image) of Rater 1

Measure	Bolus	SEM (95% CI)	Between-subject SD
Hyoid excursion	Dry, liquid, puree	4.07 percentage change (3.51, 4.64)	5.46 percentage change
Thyrohyoid approximation	Dry, liquid, puree	9.61 percentage change (8.35, 11.08)	5.29 percentage change
Tongue thickness	Apple sauce	[1.57 mm (1.15, 2.16)	4.93 mm]
	Vanilla custard	2.47 mm (1.81, 3.39)	4.96 mm
	Olive oil	1.86 mm (1.37, 2.55)	7.09 mm
GH <sup>+</sup>	-	10.52 mm <sup>2</sup> (7.75, 14.49)	65.48 mm <sup>2</sup>
FOM LAB	-	[11.48 mm <sup>2</sup> (8.39, 15.92)	23.31 mm <sup>2</sup> ]
RAB	-	7.78 mm <sup>2</sup> (8.39, 15.92)	21.34 mm <sup>2</sup>

*Note.* SEM = standard error of measurement, CI = confidence interval, SD = standard deviation, [] = assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

**Table B.6.2.** Intra-rater reliability for measurement (image) of Rater 5

Measure	Bolus	SEM (95% CI)	Between-subject SD
Hyoid excursion	Dry, liquid, puree	4.14 percentage change (3.57, 4.71)	4.05 percentage change
Thyrohyoid approximation	Dry, liquid, puree	8.09 percentage change (6.96, 9.23)	7.88 percentage change
Tongue thickness	Apple sauce	[1.41 mm (1.04, 1.95)	3.14 mm]
	Vanilla custard	1.56 mm (1.15, 2.15)	4.36 mm
	Olive oil	[2.27 mm (1.67, 3.13)	5.53 mm]
	GH <sup>+</sup> -	9.66 mm <sup>2</sup> (7.11, 13.31)	49.81 mm <sup>2</sup>
FOM	LAB -	4.33 mm <sup>2</sup> (3.16, 6.01)	21.46 mm <sup>2</sup>
	RAB -	4.72 mm <sup>2</sup> (3.47, 6.50)	20.55 mm <sup>2</sup>

*Note.* SEM = standard error of measurement, CI = confidence interval, SD = standard deviation, [] = assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

**Table B.6.3.** Inter-rater reliability for measurement (image)

Measure	Bolus	SEM (95% CI)	Between-subject SD
Hyoid excursion	Dry, liquid, puree	4.25 percentage change (3.68, 4.87)	4.46 percentage change
Thyrohyoid approximation	Dry, liquid, puree	10.26 percentage change (9.06, 12.06)	3.43 percentage change
Tongue thickness	Apple sauce	[2.37 mm (1.78, 3.40)	3.49 mm]
	Vanilla custard	2.39 mm (1.80, 3.37)	4.38 mm
	Olive oil	[2.62 mm (1.97, 3.70)	6.09 mm]
	GH <sup>+</sup> -	19.06 mm <sup>2</sup> (14.31, 27.28)	53.52 mm <sup>2</sup>
FOM	LAB -	[5.00 mm <sup>2</sup> (3.73, 7.22)	22.26 mm <sup>2</sup> ]
	RAB -	10.69 mm <sup>2</sup> (8.03, 15.33)	19.03 mm <sup>2</sup>

*Note.* SEM = standard error of measurement, CI = confidence interval, SD = standard deviation, [] = assumptions for analysis are not met, FOM = floor of mouth muscles, GH<sup>+</sup> = geniohyoid<sup>+</sup> muscles, LAB = left anterior belly of the digastric muscles, RAB = right anterior belly of the digastric muscles

## **Appendix C: A Systematic Review of Pharyngeal HRM/HRIM – Search Strategies**

### *Search strategies*

#### **MEDLINE:**

1. Deglutition/
2. swallow\*.af.
3. degluti\*.af.
4. dysphagi\*.af.
5. pharyn\*.af.
6. Esophageal Sphincter, Upper/
7. (upper esophageal sphincter or upper oesophageal sphincter or UES).af
8. impedance.af.
9. Or/1-8, 10. HRM.af.
11. High resolution manometry.af.
12. Or/10-11
13. 9 and 12.

#### **EMBASE:**

1. Deglutition/
2. deglutiti\*.af.
3. dysphagi\*.af.
4. swallow\*.af.
5. pharyn\*.af.
6. Esophageal Sphincter, Upper/
7. (upper esophageal sphincter or upper oesophageal sphincter or UES).af.
8. or/1-7
9. HRM.af.
10. high-resolution manometry.af.
11. or/9-10
12. 8 and 11
13. Deglutition/

14. deglutiti\*.af.
15. dysphagi\*.af.
16. swallow\*.af.
17. pharyn\*.af.
18. Esophageal Sphincter, Upper/
19. (upper esophageal sphincter or upper oesophageal sphincter or UES).af.
20. impedance.af.
21. or/13-20
22. HRM.af.
23. high-resolution manometry.af.
24. or/22-23
25. 21 and 24
26. 25 not 12

CINAHL:

- S1: (MH “Deglutition”) OR (MH “Deglutition Disorders”)
- S2: (MH “Swallowing Therapy”
- S3: deglutit\* OR swallow\* OR dysphagi\*
- S4: (MH “Pharyngeal Diseases”) OR (MH “Pharyngeal Muscles”) OR (MH “Pharyngeal Neoplasms”)
- S5: pharyn\*
- S6: upper esophageal sphincter OR upper oesophageal sphincter OR UES
- S7: impedance
- S8: S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
- S9: “high resolution manometry”
- S10: HRM
- S11: S9 OR S10
- S12: S8 AND S11

Cochrane Library:

High-resolution manometry

HRM

HRM AND pharyn\*

HRM AND upper esophageal sphincter

HRM AND upper oesophageal sphincter

HRM AND UES

HRM AND degluti\*

HRM AND dysphagi\*

HRM AND swallow\*

Impedance AND HRM



## Appendix D.1: Behavioural Manipulation of the UES - Questions

### Questions Task A

Research ID:			
Session	Date	Was there anything which was helpful to increase pressure?	Was there anything which was helpful to decrease pressure?
1			
2			
3			
4			
5			
6			
7			
8			
9			
		a) Was there anything which was most helpful to increase pressure? Was there anything which was most helpful to increase pressure overall?	a) Was there anything which was most helpful to decrease pressure? Was there anything which was most helpful to decrease pressure overall?
10			

## Questions Task B

Research ID:		
Session	Date	Was there anything which was helpful to increase the duration of the dark blue period?
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		<p>a) Was there anything which was helpful to increase the duration of the dark blue period?</p> <p>b) Was there anything which was most helpful to increase the duration of the dark blue period overall?</p>

## Appendix D.2: Behavioural Manipulation of the UES – Malfunctioning Sensors

**Table D.2.1.** Number of malfunctioning pharyngeal sensors included in data analysis (Exploratory Study 1)

Participant	Session 1	Session 5	Session 10	Post-training
1	0	0	0	0
2	0	0	0	0
3	0	0	1	3
4	0	0	0	1
5	0	0	0	0
6	0	0	0	0

**Table D.2.2.** Number of malfunctioning sensors included in data analysis for the pharyngeal outcome measures (Exploratory Study 2)

Participant	Session 1	Session 5	Session 10	Post-training
1	0	0	0	0
2	0	2	0	0
3	1	1	1	1
4	0	0	0	0
5	0	0	0	0
6	1	0	1	1